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General Medicine

The Treatment of Bacterial Endocarditis — ORGAIN, EDWARD S. AND DONEGAN, CHARLES K. — *Annals of Internal Medicine*, 32: 1099 (June) 1950.

An analysis of 138 instances of bacterial endocarditis is presented. This report represents the total experience of the authors' hospital in the treatment of this disease by various methods.

"During the pre-sulfonamide period (1930 to 1937), when therapy was nonspecific and unsatisfactory, 41 instances of bacterial endocarditis were observed. Of these 1 patient survived following the use of autogenous vaccine therapy.

"In the sulfonamide period (1938 to 1943), the diagnosis of bacterial endocarditis was made in 51 instances. Treatment with one or more of the sulfonamides was administered to 41 patients. Four patients survived, a recovery rate of 10 per cent. Of 24 patients who received the sulfonamides, 2 are well; of 17 patients who received the combination of sulfonamide and fever therapy, 2 were cured."

"During the penicillin period of therapy (1944 to 1947) the diagnosis of bacterial endocarditis was made in 44 patients. Six of these patients failed to receive penicillin because they refused to remain for treatment, preferred to be treated at home, or died before therapy was instituted." One patient was cured by ligation of a patent ductus arteriosus without chemotherapy. The remaining group of 37 patients was treated with penicillin, of whom 20 patients were cured.

"The ages of these 37 patients varied between 16 and 68 years; 27 were males and 10 were females.

"Thirty-two patients had mitral or aortic lesions or combinations of the two valvular lesions. Three had congenital intraventricular septal defects. One had a ligated patent ductus (that had previously been ligated for bacterial endocarditis); 1 had no detectable valvular lesion on physical examination, and 1 had an infected left auricular thrombus.

"Of the 37 patients treated with penicillin the infecting organisms were *Streptococcus viridans* in 31 patients. In the remaining 6 patients the organisms found were as follows: pneumococci in 3 instances, none of which were typed, nonhemolytic *Staphylococcus aureus* in 1, both hemolytic and nonhemolytic *Staph. aureus* in 1, and hemolytic *Staph. aureus* in 1. Of the 20 patients who were cured, 17 were infected with *Strep. viridans*, 2 with pneumococci and 1 with both hemolytic and nonhemolytic *Staph. aureus* organisms."

"The method of administration of penicillin generally combined a continuous intravenous drip with intermittent intramuscular injections. The usual schedule consisted of a continuous intravenous drip during the day for the first week with intermittent intramuscular injections every three hours during the night. After the first week intermittent intramuscular injections every three hours day and night replaced the intravenous route. During 1944, penicillin therapy was initiated in 12 patients and each received a course of sulfonamide after the completion of penicillin therapy." Of these, 4 patients recovered; each received an initial daily dose of 200,000 units of penicillin. "Of the remaining 8 patients in the failure group, therapy was begun in 6 at levels below 200,000 units per day.

"During the year 1945 and thereafter as penicillin became more plentiful, patients were treated with 200,000 to 500,000 units per day. When penicillin became available in unlimited quantities, considerably larger dosages of penicillin were administered, particularly in those cases which were initially unresponsive to penicillin therapy or whose organisms were

found to be penicillin resistant." During this period therapy was initiated in 25 patients, of which 16 were cured.

"Of the entire group of 20 patients who were cured, 9 received 200,000 units of penicillin per day; 6 patients received 400,000 to 500,000 units per day; and 5 patients received from 980,000 to 5,000,000 units per day. These figures represent maximum daily dosages. The total dosages were as follows: 8 received less than 10,000,000 units of penicillin; 4 patients received 10,000,000 to 20,000,000 units; 5 patients received 25,000,000 to 51,000,000 units; and 3 patients received 64,000,000 to 121,000,000 units as their total dosage.

"Of the 19 cures that are living, 10 have been well for more than two years; 3 patients have been well for one to two years; and 6 have been well for at least six months." One case presented evidence of healed bacterial endocarditis at postmortem examination.

"Three well patients received one or more courses of penicillin because of a recurrence of positive blood cultures while under sulfonamide therapy after cessation of penicillin treatment. Two patients were taught to administer penicillin to themselves at home in order that they might receive penicillin over prolonged periods of time in an effort to control their disease, even though a cure might not be effected. After a period of several months of successful progress, penicillin was decreased gradually to 25,000 units per day and recovery ensued." One case received penicillin for 330 days out of 365 consecutive days. One case received penicillin for 287 days out of 297 consecutive days. "Both have been well for 25 months.

"Failures have been observed in 17 patients treated with penicillin. It has not been possible to determine the cause of treatment failure in each individual instance. The first 4 patients of the series were treated with obviously inadequate doses of penicillin when this drug was quite scarce. Many of the patients have died at home without adequate observations. It seems quite probable that fatal emboli, pulmonary cerebral or general, have been the most frequent causes of death." Two failures have gone to other clinics and have been treated with tremendous amounts of penicillin (2,000,000 and 20,000,000 units per day) with the same fatal outcome. Eight patients were presumed to be cured only to relapse in a few days on discontinuing antibiotic therapy, and 5 of these were failures even after repeated courses of therapy. An analysis of the failures offers the promise that larger initial doses of penicillin might have been effective had they been instituted before the development of penicillin resistance by the organism.

The route of administration of penicillin makes little difference in the final results of therapy. "The comfort of the patient should be considered when the initial choice is made. Patients have recovered following the use of daily injections of penicillin in peanut oil and beeswax and even the oral administration of penicillin. . . . The oral administration of penicillin is not practical if high plasma levels of penicillin are required in dealing with resistant organisms.

"Sensitivity studies with the infecting organisms in vitro are extremely important before instituting therapy in order to estimate more accurately the effective daily dosage of penicillin."

"There is sufficient evidence that a bacterial organism may develop increasing resistance to penicillin so that it becomes of paramount importance to provide adequate dosage in the initial plan of therapy. If the patient with bacterial endocarditis is started on inadequate dosage, the chance of recovery may be jeopardized and treatment prolonged unnecessarily.

"The daily dosage of penicillin should depend on the sensitivity of the organism and whether the patient has had previous therapy."

"Intravenous paraamino hippurate has been used in conjunction with penicillin in the treatment of subacute bacterial endocarditis to enhance the penicillin blood level. Paraamino hippurate has been limited in its usefulness because of the necessity of administering large amounts by constant intravenous infusion.

"More recently caronamide has been administered orally with penicillin in order to increase the penicillin plasma level." One case received 24 Gm. of retentin (a form of caronamide) a day for nine days in conjunction with 50,000 units of peni-

cillin given every two hours by intramuscular injection. "During the retentin therapy the patient remained quite nauseated and values obtained one hour after a penicillin injection ranged between 0.6 and 0.8 unit of penicillin per cc. of plasma. After discontinuing retentin the level varied between .55 and .65 unit of penicillin per cc. of plasma. In this single instance retentin therapy was not helpful."

Anticoagulant therapy offers no significant advantage in the treatment of bacterial endocarditis and may be dangerous.

In this series, the duration of penicillin treatment depended on the general condition of the patient, the penicillin sensitivity of the infecting organism, and whether the patient had received previous antibiotic therapy. "The duration of penicillin therapy in the group of cures was: three weeks or less in 3 patients, three to four weeks in 4 patients, four to six weeks in 7 patients, and more than six weeks in 7 patients. Ten of the 17 failures received more than six weeks of penicillin therapy. At present, four to six weeks of penicillin therapy are being given in order to be conservative."

Khellin. New Coronary Vasodilator— Díaz, L. Calandre — *Boletín del Instituto de Patología médica*, 5: 63 (April) 1950.

Khellin is a coronary vasodilator similar in action to trinitrin and amyl nitrite, but with much more lasting results. It is obtained from *Ammi visnaga*, a plant of the Umbelliferae family, from the Mediterranean countries. In Arabia, an infusion made from the seed, has long been a popular remedy for renal colic.

The scientific study of *Ammi visnaga*, however, has a recent history. A laboratory worker in Cairo not only had angina pectoris, but also suffered with biliary lithiasis. Having treated the latter with his customary remedies without noting any relief, he resorted to tincture of *Ammi visnaga*, which was also a popular remedy for such disturbances. On the seventh day he expelled some calculi which relieved his renal disturbances and also relieved the angina crises. He attributed his improvement to the expulsion of the calculi, but several days later his angina pectoris returned. Commenting on his experience to his co-workers, he was advised to continue treatment with the tincture of *Ammi visnaga*. Improvement was immediately noted. Each time, however, he discontinued its use the precordial disturbances returned. It was decided, therefore, to investigate the action of *Ammi visnaga* on the circulatory apparatus and especially on the coronary arteries.

Three substances had already been isolated from the seeds of *Ammi visnaga*: khellin, visnagin and the glucoside of khellol.

Of these three substances, visnagin had no pharmacologic action on the coronary muscles; khellol had an action similar to khellin, but much less intense. The preparation now used has khellin as a base.

It was demonstrated that khellin acted directly on the smooth musculature with very small contractions, bringing relaxation and making the coronary arteries the most sensitive of the whole vascular system up to the point of increasing the blood flow through them as much as three or four times. It was found that it was absorbed through the intestinal tract and eliminated slowly through the kidneys.

A clinical study reported in 1949 on the treatment of angina pectoris with khellin cited the following: In 250 cases, 56 per cent responded very well; 34 per cent, moderately and 10 per cent did not respond at all to the new drug. In none of the cases, was intolerance encountered, nor did any complications develop which might be blamed on the medicament.

In 50 cases of infarct of myocardia, no definite conclusions were reached, but it was noted that the mortality seemed to be slightly less than in groups that were treated with other medicines.

Finally, in the treatment of asthma, results obtained were good, although dosage had to be higher than that required in the treatment of angina.

In the 3 cases of angina reported by the author, uniformly the results were so good that he considers khellin the best medicine discovered to date for the treatment of angina pectoris.

Briefly, the 1 case was that of a business man, 46 years old, who led a very active life. Three years previously he had first noted a sensation of precordial oppression.

One year previous to his treatment, he had an infarct of myocardia which necessitated his being in bed for three months. His next attack was accompanied by fever. Blood analysis disclosed: sedimentation 80 mm. in an hour and 10,200 leukocytes; arterial tension, max. 110, min. 80. The electrocardiogram confirmed the diagnosis of infarct. At first he was given opiates, he then began to take 150 mg. of kelicorin, the Spanish preparation of khellin. He was almost immediately relieved. As a test, the medicine was suspended and the angina pectoris returned, accompanied with great pain. After two months the patient was able to return to his home and a life of moderate activity.

Pregnenolone in the Treatment of Rheumatoid Arthritis — STOCK, J. P. P. AND MCCLURE, E. C. — *Lancet*, 2: 125 (July 22) 1950.

"In a preliminary trial, 2 women with rheumatoid arthritis and 1 man with ankylosing spondylitis were treated with Δ_5-pregnenolone. The case of ankylosing spondylitis and 1 of the cases of rheumatoid arthritis showed early objective improvement, and it was therefore decided to give this substance a more extended trial. As supplies of pregnenolone were limited, it was possible to treat only 7 further patients; and this further investigation was confined to cases of rheumatoid arthritis. The whole group consists, therefore, of 1 case of ankylosing spondylitis and 9 cases of rheumatoid arthritis.

"The criteria for the selection of cases were that the patients should be suffering from well established rheumatoid arthritis of at least one year's duration, and that the disease should be active as evidenced by pain, soft tissue swelling, and a blood sedimentation rate (B.S.R.) consistently raised above 25 mm. in one hour (Westergren). . . . Except for the patient with ankylosing spondylitis, all remained in hospital under close supervision throughout the trial; and the 7 cases in the more extended trial were observed in hospital for one month before treatment was begun."

"After the initial period of observation, all the patients received pregnenolone intramuscularly in an initial dose of 300 mg., followed by 200 mg. daily. In the 7 cases treated during the second stage of the trial this treatment was continued for three weeks. At the end of this period, injections of oil containing no pregnenolone were substituted, as a control. This was done without the knowledge of the patients or of the nursing staff who were giving the injections. This 'control' injection was continued once daily for two weeks. A second period of pregnenolone injections was then started, and this time the pregnenolone was given in combination with ascorbic acid (1 Gm.) and hyaluronidase (1,000 units), all three being administered simultaneously from the same syringe. These injections were continued for a further two weeks.

"It was decided to employ a 'control' period on the same cases in the middle of the trial rather than to have a separate series of control cases, on account of the difficulty of finding strictly comparable cases in this disease, which presents a complex clinical picture." The writers felt that if Δ_5-pregnenolone had in fact any true cortisone-like activity, any cases which had improved during the initial treatment period should show a tendency to relapse during the control period and improve again when pregnenolone injections were resumed. "Except for routine analgesics, no other therapy was employed during the trial."

"Of the 10 cases treated by intramuscular injections of Δ_5-pregnenolone, 3 showed significant, measurable, objective improvement. Two of these cases were treated during the preliminary trials (when no control period was employed). In 1 of these 2 cases—probably both—there is considerable doubt whether the improvement can be directly attributed to the pregnenolone therapy. . . . In the more extended trial, only 1 of the 7 cases showed objective improvement."

"When the more extended trial was begun, 6 of the 7 cases reported an immediate improvement. They all described appreciable reduction in pain and a subjective sense of increased motility in the affected joints which was most marked about one and one-half hours after each injection was given. With 1 exception, however, no objective change could be demonstrated with the goniometer or tape measure. One of the patients, who had

been bedridden for two years, walked a few steps with help at the end of the first week of treatment. There was, however, no convincing objective change in any of her joints, and she was unable to repeat the performance the following week despite the continuance of pregnenolone injections. Moreover, in most of the cases the subjective improvement one and one-half hours after the injections continued during the period when the control injection was being used. In no instance could the sense of subjective improvement be said to amount to euphoria, even in those cases showing objective improvement."

Reviewing the period of treatment as a whole, with the exception of 1 case, the enthusiasm of the patients was greatest during the first two weeks, and waned without obvious cause during the third week of pregnenolone administration. "It remained substantially the same during the period of 'control' injections, and certainly there was no reawakening of enthusiasm when pregnenolone injections were resumed."

"No general toxic effects were observed which could be attributed to the pregnenolone. One of the earlier cases developed a recurrent symmetrical purpuric eruption on the legs during treatment. It was clear from the history, however, that there had been one or more similar attacks before pregnenolone was administered, and the rash disappeared spontaneously despite the continuance of treatment.

"Local reactions, on the other hand, occurred in 7 of the cases and were severe in 5. These reactions, which appeared at the injection sites after a latent interval of three weeks, consisted of red, brawny, indurated swellings, which were extremely tender to touch. These swellings were very painful, and in 1 instance prevented the second course of pregnenolone injections from being given. In 4 cases the reactions first appeared at the end of the initial three weeks of pregnenolone injections and tended gradually to fade during the period of control injections. It was partly for this reason that hyaluronidase was given during the second period of pregnenolone injections. It was hoped that by hastening absorption hyaluronidase would lessen the tendency to local reaction. Unfortunately it made no difference, for reactions reappeared at fresh injection sites in each of the previous reactors one week after injections were resumed. Sensitization to the solvent has not been eliminated as the cause of these reactions, which would certainly constitute a serious objection to continued intramuscular administration of this compound by the method described."

While it would be unwise to draw any dogmatic conclusion from so small a series, it seems clear that, at least with the dosage employed, Δ_5-pregnenolone is unlikely to be widely applicable in the treatment of rheumatoid arthritis. "Whether better results would be obtained with heavier dosage is uncertain." With the technique used, it is fairly certain that local reactions would quickly prohibit any increase.

A Possible Mode of Transfer of Infection by Syringes Used for Mass Inoculation — EVANS, R. J. AND SPOONER, E. T. C. — *British Medical Journal*, 2: 185 (July 22) 1950.

"A common mass inoculation technique (M.R.C., 1945) employs a separate sterile needle for each injection, but does not sterilize the syringe, which contains several doses of inoculum, between injections.

"Accidental infections attributable to this practice do not seem to have been described, and experience generally suggests that the technique is, so far as any injection technique can be, a safe one."

It seemed, however, worth while to investigate the advantages of using a fresh needle for each injection. If there is any risk at all of syringe transmission, the possibility, however remote, should be evaluated as accurately as circumstances permit.

"Experiment 1.—This first experiment was therefore made with mice and virulent pneumococci. The virulence of a smooth strain of *Streptococcus pneumoniae* type I was assured by three mouse to mouse passages. Twenty-four mice were then inoculated intraperitoneally with diluted peritoneal washings from a dead animal. Next day, 9 were dead and the remainder were sick. Thirteen which appeared moribund were killed and used immediately in the experiment.

"The plan was to fill a sterile syringe with 1 ml. of sterile broth, to inject 0.1

ml. intraperitoneally into 1 of the recently killed pneumococcal mice, to change the needle and to inject 0.2 ml. of broth into a normal mouse, and then, the needle having been changed again, to inject 0.5 ml. into the same infected mouse's peritoneal cavity; finally, after a third needle change, to inject the remaining 0.2 ml. into a second normal mouse. One normal mouse was therefore injected from a syringe which had delivered 0.2 ml. into an infected animal, and a second normal mouse from the same syringe after delivery of 0.1 and 0.5 ml. into the infected mouse. Two normal mice and 1 infected mouse were thus injected from one syringe, the needle being changed after each injection.

"This procedure was adopted because it was thought that the second injection of 0.5 ml. into the infected mouse might produce a higher intraperitoneal pressure and so a bigger change of reflux of infected fluid into the syringe.

"Nine 1-ml. syringes of various makes were used, and 40 needles, sizes 15 and 17. All were oven-sterilized initially; resterilization during the experiment was achieved by boiling. In order to minimize as far as possible the risk of cross infection occurring between the infected and the normal mice, the conduct of the experiment was divided into three tasks, each of which was performed by one operator alone.

"The first operator killed the infected mouse by breaking its neck, and pinned it out belly upwards on a cork mat ready for the second operator.

"The second operator handled the syringes and made all the injections. He performed the following operations in strict sequence: (1) filled a sterile syringe to the 1-ml. mark with sterile broth; (2) injected 0.1 ml. of broth intraperitoneally into an infected mouse; (3) disconnected the needle from the syringe and placed it in the sterilizer; (4) fitted a sterile needle to the same syringe and then injected 0.2 ml. of broth intraperitoneally into a normal mouse; (5) discarded the second needle into the sterilizer, fitted a fresh sterile needle to the syringe, and injected 0.5 ml. of broth intraperitoneally into the same infected mouse as at stage 2; (6) discarded the third needle to the sterilizer, and, after fitting a fresh sterile needle to the syringe, injected the final 0.2 ml. of broth intraperitoneally into a second normal mouse; and (7) discarded the syringe and needle to the sterilizer.

"The sequence of operations was repeated for each of the 13 infected mice, and, in all, 26 normal mice were inoculated in this way. No attempt was made to clean or sterilize the belly walls of the mice. Injections were made in the usual manner. Care was taken not to withdraw the plunger of the syringe after giving the injection. No reflux into the syringes was observed.

"The third operator handled the normal mice, holding them for injection, and placing them after injection into cages so that mice inoculated at stage 4 were caged together, labelled '0.1 ml.,' and those inoculated at stage 6 were caged together, labelled '0.5 ml.'

"By the morning after injection, 5 of the 26 'normal' mice were dead. Fourteen more died in the course of the next 48 hours. . . . Blood agar cultures and stained films prepared from the heart blood of each dead mouse showed abundant pneumococci. The 7 surviving experimental mice were alive and in apparently good health three days after injection.

"It appeared from this experiment that a change of needle gave very little protection against the carry-over of infection from infected to normal mice.

"Experiment 2.—Later, the experiment was repeated, using mice of a different strain and four 1-ml. glass-metal Record syringes together with five 1-ml. all-glass tuberculin syringes. One of the Record syringes was reboiled during the experiment and used a second time. In this second experiment procedure was simplified, the steps of the operation being as follows: (1) Record syringes were sterilized by boiling, all-glass syringes by hot air sterilization; (2) the syringe was filled with 1 ml. of sterile broth; (3) 0.1 ml. of broth was injected intraperitoneally into a normal control mouse; (4) 0.1 ml. of broth was then injected intraperitoneally into a 'pneumococcal' mouse killed immediately beforehand by neck-breaking; (5) the used needle was removed and discarded and a fresh sterile needle fitted to the syringe; and (6) 0.1 ml. of broth was then injected intraperitoneally into each of two normal mice.

"As they were injected the mice were caged in 6 separate groups of 5 mice—'Record' and 'tuberculin' controls, 'Record' and 'tuberculin' first and second test mice.

"During the next 48 hours all control mice remained in good health, but 16 of the 20 test animals developed a fatal pneumococcal peritonitis and septicaemia, which was confirmed by culture and smear."

"These mouse experiments were intended to simulate the ordinary technique of mass inoculation carefully performed. As a test of transfer of infection they were however, very sensitive, because the number of virulent organisms needed to produce pneumococcal septicaemia in the mouse is very small, and the peritoneal cavities of the pneumococcal mice used contained very large numbers of pneumococci.

"An attempt has therefore been made to assess the risk of carry-over of micro-organisms in the 'separate needle, common syringe' technique of inoculation by means of quantitative experiments using bacterial cultures instead of pneumococcal mice.

"Experiments 3 to 5.—These were performed with an 'artificial mouse' consisting of a length of glass tubing bent at a right angle, the shorter arm being fitted with a 2-inch (5-cm.) length of rubber tubing, plugged at the far end with a glass rod. Overnight broth cultures of *Shigella flexneri* (Y6R or NCTC 4832) were pipetted into the tube, filling the rubber and the horizontal glass limb, and rising in the vertical limb to a height which determined the hydrostatic pressure inside the rubber tube. Six syringes were employed in each of these experiments—1-ml. all-glass 'tuberculin' syringes in experiments 3 and 4, and, in experiment 5, four 1-ml. 'Record' syringes and two all-glass 'tuberculin' syringes.

"The pattern of the three experiments was the same. The sterile syringe having been filled with sterile broth, 0.1 ml. was injected through the rubber tube into the 'artificial mouse.' The needle was then withdrawn. It was changed and not changed on alternate syringes, even-number syringes not having their needles changed, odd-number syringes receiving a fresh sterile needle before the next step in the experiment, which was to discharge 0.2 ml. of broth from the syringe into each of three tubes containing 0.8 ml. of sterile broth. From these tubes suitable dilutions were prepared, and six-plate surface counts of their contained bacteria were made."

"Two of the nine tests in which the needle was changed showed no carry-over of infection, but in the remaining seven, change of needle showed very little advantage over the nine tests in which the needle was not changed.

"The height of the fluid column in the vertical limb of the 'artificial mouse' in these experiments varied between 2 and 6 cm. There was no apparent correlation between height of fluid column and result. However, it seemed possible that the positive pressure against which the first injection was made might be forcing culture along the needle, although no plunger movement was evident. To test this, another experiment was performed.

"Experiment 6.—In this experiment the procedure was similar except that, instead of injecting through rubber into culture under a few centimetres head of pressure, the first injection was made into a small volume of culture held in a small bottle, the point of the injecting needle being held 1 or 2 mm. below the surface, and the syringe necessarily at an angle with the horizontal, such that the pressure on the broth in the syringe must throughout have been greater than the pressure in the culture around the needle point. . . . One out of three syringes in which the needles were changed still showed a considerable carry-over of bacteria. In this experiment, as in all the preceding ones, the injection into the infected mouse or culture had been made without emptying the syringe. It seemed possible that, unless the plunger were pushed home against the bottom of the syringe, small plunger movements might cause a reflux into the needle.

"Experiment 7.—In this experiment injection was not made into the infected material. Instead, each sterile syringe was first washed out with a small volume of sterile broth and emptied. The point of the needle was then dipped into a culture of *S. flexneri* to a depth of 1 or 2 mm., after which it was withdrawn and the needle was changed. A small volume, up to 1 or 2 ml., of sterile broth was drawn

into the syringe through the new needle. Three drops were then expelled on to an agar plate and spread with a sterile spreader.

"Sixteen syringes were used, ranging from 1 ml. to 10 ml. in capacity, and of various makes. They were fitted with needles of differing lengths and bore. Next day 2 of the 16 plates showed numerous colonies of *S. flexneri,* the remaining 14 showing none.

"This experiment shows that if the needle point is contaminated, even when the syringe is empty and with the plunger pushed home and not moved, and even when there is no appreciable pressure forcing infected fluid back into the needle, it is still possible for the syringe to become contaminated when the needle is changed. It is clear, however, that the frequency of such contamination was less than in those experiments in which the plunger was moved, or in which injections were made into infected fluid under a small head of pressure.

"Experiment 8.—A final experiment was performed to help separate these two factors of plunger movement and pressure of infected fluid. The 'artificial mouse' used in experiments 3 to 5 was employed again, but this time the injecting syringe contained only about 0.1 ml. of fluid, the whole of which was injected through the rubber, so that at the end of the injection the plunger was 'home' against the bottom of the syringe.

"One 'artificial mouse' was used to test four syringes. Sixteen syringes in all, of various sizes and patterns, from 1 ml. to 10 ml. in capacity and fitted with various needles, were tested using 4 'artificial mice.' The order of procedure was: (1) Sterile broth was drawn into the syringe and discharged until about 0.1 ml. remained in the syringe. (In 1-ml. and 2-ml. syringes this volume could be measured easily. In 5-ml. and 10-ml. syringes it was judged by eye, and checked by the change in height of fluid column noted after its injection into the 'artificial mouse.') (2) This terminal volume of broth was then injected through the rubber into the culture of *S. flexneri* and the rise in height of fluid column noted. (3) The needle was then discarded, being replaced by a fresh sterile needle. (4) About 0.5 ml. of broth, sterilized in a small individual tube, was then sucked into the syringe through the new needle. (5) Three drops were then discharged on to the surface of an agar plate and spread with a sterile glass spreader."

Next morning, after overnight incubation at 37° C., 3 of the 16 plates showed no growth, but the remaining plates showed colonies of *S. flexneri,* checked by slide agglutination, varying in numbers from six to several hundreds.

"The experiments here reported show that contaminants on the needle point, even when no injection is made and when the contamination is derived from fluid under negligible hydrostatic pressure, may travel back along the needle and contaminate the syringe when the needle is removed from it. Without further extensive quantitative experiments, it would not be possible to assess the frequency with which this happens; probably the pattern of syringe and of needle would affect the degree of risk.

"It is likely, from the experiments reported, that small movements of the plunger and the hydrostatic pressure around the needle tip are factors which increase the risk of syringe contamination; and, of course, both of these factors are involved whenever any injection is given.

"If, as appears from experiments 6 and 7, contamination of the needle tip can lead to contamination of the syringe, though the pressure around the needle tip is not significantly raised, then some explanation of the passage of the contaminant back from the needle tip to the syringe nozzle must be sought. The most probable explanation seems to be that . . . . withdrawal of the nozzle of the syringe from the socket of the needle may suck fluid back from the lumen and point of the needle to contaminate the point of the syringe nozzle. Measurement of the length and internal diameter of some of the needles used in these experiments indicated that the lumen volume varied between 2.5 and 5.8 c.mm. for small needles of the kind usually employed for subcutaneous and intramuscular injection. These volumes are probably smaller than the displacement volume of the syringe nozzle in the needle socket."

The "separate needle, common syringe" technique might transfer infection from one subject to the next if the tissue into

which the first injection was made were itself infected. Experiments indicate, however, that syringe contamination does not always follow removal of a contaminated needle, and therefore the "separate needle, common syringe" technique is safer than the use of one needle and syringe for inoculation of several subjects.

"The actual risk of syringe transmission of infection during mass immunization is evidently a very small one, because it depends not only on the imperfection of the syringe technique but also on the probability that muscle, skin, or subcutaneous tissue may harbour an infective agent capable of being transmitted.

"Where bacterial infections are concerned the risk is probably very small. An injection made into a subject with an undetected incipient septic lesion might cause, by syringe contamination, lesions in several subjects subsequently inoculated, and all the lesions, including that which in fact caused the infections, might be wrongly attributed to prior contamination of the injection material." The possibility that poliomyelitis or other neurotropic viruses may exist in relatively high local concentrations in the nerves lying in muscles or in skin or subcutaneous tissues cannot, in the authors' view, be entirely excluded, although on the evidence available this seems an unlikely explanation of the association between poliomyelitis and inoculations.

"The hazards of the 'separate needle, common syringe' technique may well be greater in countries where malaria and blood-borne viruses are more frequent."

An Outbreak of Syringe-Transmitted Hepatitis with Jaundice in Hospitalized Diabetic Patients — SHERWOOD, PAUL M. — *Annals of Internal Medicine*, 33: 380 (August) 1950.

"The transmission of hepatitis by means of contaminated syringes has been recognized and described only within the past few years. Despite the frequency of the reports, not all medical personnel who give injections are aware of the possibility of disseminating the virus of hepatitis by failure to use a properly sterilized individual syringe and needle for each patient, regardless of the route of the parenteral administration. The use of one syringe with fresh sterile needles for the drawing of venous blood from several patients, and the injection technic which employs a single syringe with simple change of needle for each patient inoculated ('multiple dose per syringe method'), provide the setting for the inadvertent transmission of viral hepatitis."

The occurrence of jaundice within a 10 week period in 4 diabetic patients at the writer's hospital was observed. "Although the spontaneous occurrence of infectious hepatitis in these patients cannot be excluded, it was believed to be a syringe-transmitted outbreak. All 4 patients developed the clinical picture of acute viral hepatitis and recovered within a period ranging from 13 days to 46 days. The laboratory and roentgen ray findings corroborated the diagnosis of acute viral hepatitis. No case of 'sporadic' infectious hepatitis was observed on the medical wards during this time.

"Case Reports.—Case 1: A 50 year old diabetic white male had been a domiciliary patient since April 30, 1948, and had received 45 units of protamine zinc insulin daily from Medical Unit A.

"On August 7, 1948, he was admitted to the hospital because of weakness, nausea, glycosuria and acetonuria. With fluids, diet and supplementary insulin he soon improved. He was hospitalized for a period of 16 days, during which time insulin was administered to him from Medical Unit B. He was returned to domiciliary care on August 23, 1948, on a diabetic diet and again received his insulin each morning from Medical Unit A.

"On September 29, 1948, the patient was readmitted to the hospital because of anorexia and jaundice. He had been feeling ill with no definite complaints for 10 days prior to admission and had noted a weight loss of 3 pounds.

"Complete examination disclosed normal findings except for icteric scleras and tenderness in the right upper quadrant of the abdomen. The temperature was 98.2° F., pulse 88 and the blood pressure 114/68 mm. Hg.

"The urine showed a specific gravity of 1.030, sugar 4 plus, negative for albumin and acetone and negative microscopic findings. The serological test for syphilis was negative. The red blood cell count was

4,090,000, with 75 per cent hemoglobin. The white cell count was 8,900, with 61 per cent neutrophils and 37 per cent lymphocytes. The nonprotein nitrogen was 29; serum chlorides, 665. Serum bilirubin was 0.5 mg. (1 minute direct), cephalin flocculation was 3 plus (48 hours) and alkaline phosphatase was 3 units (Bodansky). The sedimentation rate was 27 mm. in 60 minutes (Cutler).

"Gastrointestinal series showed roentgenologically normal esophagus, stomach and duodenal bulb. Barium enema was negative.

"While in the hospital his diabetes was controlled by diet and 40 units of protamine zinc insulin and 10 units of crystalline insulin administered daily at Medical Unit B. His appetite gradually improved, the scleral icterus disappeared, and tenderness in the right upper quadrant of the abdomen was no longer present. On October 12, 1948, the icteric index was 11 units and the serum bilirubin had fallen to 0.2 mg. He was discharged from the hospital on October 25, 1948.

"Follow-up examination on February 9, 1949, revealed that he had been asymptomatic since discharge and that his diabetes was well regulated. The icteric index was 8 units. The bromsulfalein test (5 mg. per Kg.) showed no retention of the dye at 45 minutes.

"Case 2: A 51 year old white male with progressive muscular dystrophy and diabetes had been hospitalized here continuously since July 22, 1948. His diabetes was satisfactorily controlled by diet and 35 units of protamine zinc insulin and 30 units of crystalline insulin, administered daily at Medical Unit B.

"On October 26, 1948, he was noted to have an icteric appearance to his skin and scleras. Anorexia and malaise were minimal. Although the constitutional symptoms diminished rapidly the jaundice increased in intensity and the liver became tender and palpable 8 cm. below the right costal margin.

"The red cell count was 4,240,000, with 75 per cent hemoglobin. The white cell count was 5,200, with 65 per cent neutrophils and 29 per cent lymphocytes.

"On October 28, 1948, the icteric index was 50 units and in two days rose to 100 units. By November 8 it had fallen to 50 units. The cephalin flocculation was 4 plus and the alkaline phosphatase was 3.2 units. On January 6, 1949, the icteric index was 20 units and the cephalin flocculation was 2 plus. On February 7, 1949, the icteric index was 15 units.

"A gastrointestinal roentgen ray series on November 2, 1948, showed a normal esophagus, stomach and duodenum. There was no widening of the duodenal loop and no reversed E effect was noted.

"By November 21, 1948, his hepatitis was asymptomatic and complete examination revealed clinical clearing of jaundice with retreat of the liver beneath the costal margin. He had been afebrile throughout the course of his illness.

"Case 3: A 71 year old obese white male with hypertensive arteriosclerotic cardiovascular renal disease and diabetes mellitus (and probable intercapillary glomerulosclerosis) had been a hospital patient here since April 2, 1948. His regimen, in addition to maintenance digitalization, consisted of a low caloric diabetic diet, 45 units of protamine zinc insulin and 35 units of crystalline insulin, administered daily at Medical Unit B.

"On November 11, 1948, he complained of malaise and anorexia. Three days later jaundice became apparent and the liver, previously not felt, was 5 cm. below the right costal margin and tender. His stools were light yellow in color.

"The red cell count was 4,030,000. The white cell count was 8,800, with 61 per cent neutrophils and 38 per cent lymphocytes. On November 14, 1948, the icteric index was 100 units, the serum bilirubin 6 mg., and the alkaline phosphatase 2.8 units. Two weeks later the icteric index remained at 100 units, the serum bilirubin was 5 mg., alkaline phosphatase was 2.8 units, and the cephalin flocculation was 3 plus. The icteric index was 85 on December 1, and the serum bilirubin decreased within a few days to 2 mg. On January 20, 1949, the icteric index was 9 units and the cephalin flocculation was 3 plus.

"His appetite was improving on November 30, 1948, the icterus was clinically subsiding, and his stool was darker in color. The diabetes was well controlled. He had remained afebrile throughout. By December 21, 1948, there was marked

improvement and the liver edge was felt at the costal margin. The icterus had clinically disappeared on December 29, 1948.

"Case 4: A 51 year old white male with diabetes was a domiciliary patient at this institution. From June 14, 1948, to September 28, 1948, he received 40 units of protamine zinc insulin and 10 units of crystalline insulin administered daily at Medical Unit A. He left the institution on September 28, 1948, but again returned for domiciliary care on November 12, 1948. From November 12, 1948, to December 7, 1948, he received no insulin, in an attempt to regulate his diabetes on diet alone.

"He was admitted to the hospital on December 7, 1948, with the history of malaise, anorexia, weakness and vomiting. The urine had been dark and the stools light for three days, and on the day of admission he had noted scleral icterus. He denied chills, fever, pain or weight loss.

"Physical examination revealed normal findings except for icterus of the skin, scleras and mucous membranes, and a nontender liver with the lower anterior border 10 cm. below the right costal margin.

"The temperature was 98.6° F., the pulse 88, and the blood pressure 130/88 mm. Hg.

"The serological test for syphilis was negative. The red cell count was 4,560,000, with 80 per cent hemoglobin. The white cell count was 9,500, with 72 per cent neutrophils and 25 per cent lymphocytes.

"The icteric index on admission was 150 units and the serum bilirubin 12 mg. The cephalin flocculation was 4 plus. On December 29, 1948, the icteric index was 30 units and the serum bilirubin was 2 mg. Total cholesterol was 184 mg. Cephalin flocculation was 3 plus. Total proteins were 6.75 Gm., albumin 3.89 and globulin 3.05.

"His diabetes was readily controlled by diet and 30 to 40 units of protamine zinc insulin, supplemented by 15 to 20 units of crystalline insulin daily. His icterus appeared to clear substantially by December 28, 1948, and was clinically absent by January 22, 1949. The liver edge likewise receded. He was asymptomatic after his third hospital week."

"When the mode of insulin administration for these patients was investigated, it was found that a single diabetic syringe was used each morning for the protamine zinc insulin and another for the crystalline insulin, with a change of needle for each patient. The vial of insulin was often reentered with a fresh sterile needle attached to the previously used diabetic syringe.

"Venipunctures for blood sugar determinations, however, were performed with a sterile syringe and needle for each patient.

"Throughout the time covered by this report, there were 4 diabetic patients in the domiciliary portion of the institution who were receiving insulin by the method described above from Medical Unit A. Case 1 was 1 of these, except from August 7, 1948, to August 23, 1948, when he was hospitalized for the regulation of his diabetes. During his hospital stay he received his insulin by the same syringe technic from Medical Unit B. Of the 5 other hospitalized diabetic patients receiving insulin from Medical Unit B, 2 developed jaundice. The remaining 3 diabetic hospital patients, although exposed to syringe transmission of an icterogenic agent during more than one period, showed no jaundice or evidence of anicteric hepatitis.

"It appears likely that case 1 was in the incubative stages of his hepatitis during his first hospital stay in August, 1948. Both case 2 and case 3 presumably received icterogenic serum at that time and developed jaundice within a period of 64 days to 99 days later.

"Upon analysis, case 4 was found to have been exposed to syringe-transmitted hepatitis at two periods, June 14, 1948 to August 7, 1948, and August 25, 1948 to September 29, 1948. The range of the incubation time for the former period was 122 to 176 days; for the latter, it was 70 to 106 days.

"The 2 other domiciliary patients receiving insulin from Medical Unit A did not contract jaundice or develop evidence of hepatitis, despite exposure during more than one period. It is noteworthy that the course of the acute hepatitis with jaundice in these hospitalized diabetic patients was generally uneventful. No complications were encountered, no deaths occurred and the diabetes was not difficult

to control. The nature of the outbreak was recognized as syringe-transmitted hepatitis on November 14, 1948. All partially used vials of insulin were immediately discarded and all injections were thereafter given by autoclaved separate syringe and needle."

"The clinical distinction between infectious hepatitis and homologous serum jaundice is usually based on the length of the estimated incubation period, the route of infection, and the presence or absence of fever. Some investigators, however, believe that the two viruses are closely allied, or that one is actually some modification or mutation of the other. In an individual case, one virus frequently cannot be differentiated from the other with certainty. It seems wise, therefore, to include them both under the term 'viral hepatitis,' unless specific immunological characteristics of either virus can be demonstrated. The absence of pathological criteria for the differentiation between the two lends support to this suggestion."

"It is important to realize that either type of the disease may be unintentionally transmitted by blood or blood products, improperly sterilized needles and syringes or multiple-dose per-syringe technic. In outbreaks of the type reported here, the length of the incubation period has been commonly used to classify the hepatitis. In general, it is believed that the incubation period for strains of the virus of infectious hepatitis given by parenteral inoculation ranges from 15 to 43 days, while that of homologous serum jaundice is 60 to 135 days."

"Many attempts have been made to focus attention on methods of prevention of this new and accidental means of transmitting disease. A reduction in the number of venipunctures performed lowered the incidence of hepatitis in one diabetic clinic." When only unsterile syringes are available for venipuncture, one writer recommends that in order to avoid sucking back blood, the needle should be withdrawn before releasing the tourniquet. "It seems that the preferable method under these circumstances would be to collect blood by use of a needle alone. Even needles or lancets used for multiple finger punctures in the laboratory must come in for greater scrutiny." Since any laboratory procedure carries with it the risk of contracting viral hepatitis if the blood is obtained with a lancet or needle merely washed with alcohol or ether, a fresh sterile needle is necessary for each puncture.

"In hospital practice, the hazard of transmission is understandably far greater. Aside from the use of blood and blood products, sporadic active cases of viral hepatitis are usually present throughout the year on medical wards. Patients in the incubation period and anicteric cases are particularly important in the spread of the disease. Many blood tests are performed. Ampules of injectable substances may be used for several patients and, if reentered by imperfect technic with a contaminated syringe, the entire contents become infective. The multiple-dose per-syringe technic has not yet been universally discarded. The resulting cases of jaundice have been aptly called 'hospital hepatitis.'

"The use of an individual sterile needle and syringe, and scrupulous care for each injection, are simple and necessary prerequisites for the eradication of this problem. Until disposable needles and syringes are commonly available, sterilization of equipment by dry heat (160° C.) for a minimum of one hour, or autoclaving or boiling for about 30 minutes, is essential. Unless this precaution is taken wherever blood collections are made or therapeutic injections are given, the potential danger of syringe-transmitted hepatitis still exists."

The Treatment of Scabies in an Institution. Comparative Study—APPEL, BERNARD — *New England Journal of Medicine*, 243: 74 (July 20) 1950.

Among newer compounds are two that have already established themselves as effective antiscabietics: the gamma isomer of hexachlorocyclohexane, available as a proprietary cream under the name Kwell, and N-ethyl-o-crotonotoluide, available as a proprietary cream under the name Eurax.

A total of 328 patients were treated in a large state mental institution. There were three large wards which the writer designated as wards A, B and C. Ward A had 99, Ward B 87 and Ward C 142 patients each.

"The obvious opportunity of employing more than one remedy as a comparison study was embraced, and it was decided to use benzyl benzoate emulsion for Ward A, Eurax for Ward B and Kwell for Ward C."

"All patients were treated exactly alike; every patient in the colony was treated, whether or not affected. Each ward was treated completely as a unit. After therapy had been completed in one ward, the next one was treated in the following week, and the next one a week later. The same team of nurses and attendants gave all the treatments under the same supervision. Each person on the treatment team was assigned to only one procedure, which was carried out as a production line operation, throughout the entire three week project."

First Day.—"In the morning, right after breakfast, a specially organized shower was given. Each patient was checked in alphabetically, undressed, soaped, showered and dried (by attendants and nurses in bathing suits actually in the shower room with the patients)."

"The patient stood on a sheet on the floor, two nurses applying the medication, liberally, by vigorous manual application to the entire body surface from the neck down, including the wrists and hands, genitals, perineum, ankles, feet and soles. The name was called off and checked after the application had been completed."

"The patient was dressed in the usual clothing, her name was checked out alphabetically, and she was sent back to the ward through a one way traffic system to prevent evasion of treatment."

Second Day.—"In the morning, right after breakfast, using the alphabetical check-in and check-out system, each patient undressed; medication was again applied liberally by vigorous manual application to the entire surface area below the neck, and then the patient was dressed in the same clothing and sent back to the ward."

Third Day.—"In the morning, right after breakfast, the organized shower was repeated. The patient was alphabetically checked in, soaped, showered and dried exactly as on the first day."

"The patient was dressed in a completely different outfit of clothing previously sterilized by autoclaving or disinfection or special sterilizing laundering, depending on the article of clothing. The clothing worn by the patient on the way in was red-tagged for processing before reissue for wearing again."

"Patients were alphabetically checked out into the recreation lounge and not permitted back into the ward. In the morning, while they were at breakfast, every bed was stripped of all linen, which was red-tagged and sent to the laundry. Then all the mattresses and pillows were sprayed with a fine mist from a pressure pump spray with 2 per cent benzyl benzoate soapy emulsion, on Ward A and Ward B; Ward C was sprayed with an emulsion of gamma hexachlorocyclohexane. A general, rapid housekeeping cleaning of the entire ward, including a wash of the chairs with 3 per cent benzyl benzoate soapy emulsion, was then given. In the afternoon, the beds were made up with fresh linen. In the evening, the patients returned to the clean ward."

"A noteworthy observation was the complete absence of post-therapeutic dermatitis, at least to any appreciable degree. This is unequivocally so with both Eurax and Kwell."

"No patients who were clear of suspicious lesions gave evidence of infection after the treatment." The exception was a patient who was clear at the beginning of the study, went home on a visit, and then manifested a most resistant, profuse, typical infection, which required a first treatment with Eurax and three retreatments with Kwell. "No patients first treated with Kwell needed retreatments. Of the patients first treated with benzyl benzoate, 3 needed one retreatment, and 1 needed two retreatments. Of the patients first treated with Eurax, 5 needed one retreatment, 1 needed two retreatments, and 1 needed three retreatments.

"Retreatments were to have been done with the same medication as the first treatment. Because of a misunderstanding, however, all retreatments were done with Kwell. It was necessary to use Kwell twice after benzyl benzoate in 1 case, twice after Eurax in 1 case and three times after Eurax in another case to achieve clinical cure. Apparently, the cases resistant to one remedy are also resistant to another."

The Problem of Streptomycin Damage — Leiblein, Hilmar — *Deutsche medizinische Wochenschrift*, 75: 898 (June 30) 1950.

The author reports the case of a girl aged 17, who was taken ill with jaundice, intense headache, and repeated vomiting; on admission to another hospital the patient showed a subfebrile temperature and definite nuchal rigidity, but no other neurologic symptoms. Spinal puncture revealed a fluid with a negative Nonne-Apelt reaction and a weakly positive Pandy reaction, with spider-web formation on standing, and containing 74 lymphocytes per cu. mm. Tuberculous meningitis was suspected and streptomycin treatment was immediately instituted; 1 Gm. was given daily intramuscularly and 60 mg. were given intraspinally at intervals of two days. After one week the spinal fluid contained 200 cells and after 12 days 33 cells; there was no spider-web formation. The streptomycin dosage was increased to 1.5 Gm. After three weeks the fluid contained 18 cells and the temperature was normal. No tubercle bacilli could be demonstrated bacteriologically. The patient's general condition was good. The patient responded to the last intraspinal streptomycin injections with vomiting, and the temperature rose. Streptomycin treatment was discontinued after a total of 24.8 Gm. because of the intense vomiting. The patient gained weight. The jaundice had subsided. However, the patient could not get up, complained of dizziness and had a staggering gait. Two months after onset diplopia appeared for the first time.

On admission, three months after onset, neurologic examination showed temporal pallor of the papilla on both sides, weakening of the corneal reflexes, anesthesia of the right trigeminal area, impairment of the auditory acuity on the right side, and total bilateral lack of vestibular function; the right limbs showed a typical hypertonic-akinetic extrapyramidal syndrome, and the right half of the body showed anesthesia. Suboccipital encephalography and percutaneous arteriography of the left carotid artery showed no appreciable pathologic findings. The spinal fluid was normal and the serologic reactions were negative. In spite of energetic medical and mechanical therapy for six weeks, the extrapyramidal syndrome of the right side showed only insignificant improvement and the optic and vestibular functions did not improve.

Clinical studies showed no signs of active or recent tuberculosis and it seems justified to rule out tuberculous meningitis. Syphilitic meningitis could also be ruled out. The patient had undergone two treatments for taenia at a short interval and apparently these treatments had resulted in liver damage and meningeal irritation; complications of this type have been reported from Filix mas preparations. However, the author is convinced that the severe neurologic symptoms were attributable to the streptomycin as the patient reacted to the intraspinal injections with vomiting and fever soon after institution of treatment, while otherwise being in good condition. Cathie demonstrated that streptomycin irritates the normal meninges while it is well tolerated in inflammatory conditions. The signs of hypersensitivity appeared at a stage when the primary meningitis phenomena had already largely regressed. The author believes that the massive neurologic permanent damage was caused by the intraspinal streptomycin injections and that such disturbances are produced by penetration of the streptomycin into Virchow-Robin's spaces, with disseminated toxic damage to the ganglion cells at the cerebral base.

Streptomycin treatment requires an accurate indication. Naturally in a suspicious case valuable time until the results of a culture can be obtained should not be lost, however it is extremely important to use all diagnostic methods for clarification as fast as possible; spider-web formation is not pathognomonic of tuberculous meningitis although most frequent in this affection. It seems worthy of special consideration whether it is necessary in a case of suspected tuberculous meningitis to start immediately both intramuscular and intraspinal or intracisternal streptomycin treatment; according to Cathie only small amounts of intramuscularly injected streptomycin penetrate into the cerebrospinal fluid when no meningitis is present, while the conditions for diffusion are extremely favorable in the presence of meningitis. It has been stressed that further diagnostic

evaluation of the spinal fluid becomes impossible when a meningitis from physical or chemical causes is superimposed on the primary bacterial one, and thus cases occur in which one cannot decide to discontinue the antibiotic, and thereby unnecessary exposure to streptomycin damage is created. Particularly Anglo-American authors have increasingly taken a stand against intraspinal streptomycin treatment. In cases suspected of tuberculous meningitis it seems indicated to combine intramuscular streptomycin treatment with tuberculostatic chemotherapy, as this combination leads to multiplication and potentiation and not merely to summation of the therapeutic effects, and to omit immediate intraspinal or intracisternal streptomycin treatment for diagnostic reasons and because of the danger of streptomycin damage.

Effectiveness of Newer Drugs in Seasickness — WRIGHT, WAYNE L. — *United States Armed Forces Medical Journal*, 1: 570 (May) 1950.

"The medications used in this study were Army Motion Sickness Preventive, benadryl, dramamine, and placebos."

"The investigation was divided into two phases: therapeutic and prophylactic.

"In the determination of the therapeutic value of the drugs, no presailing medication was given to any passenger. Therapy was begun only when the person reported to sick bay with symptoms of motion sickness. The first 4 persons seen were given placebo, M. S. P., benadryl, and dramamine respectively in that order, and the routine repeated with each succeeding 4 persons. Each person was instructed to take 1 tablet immediately and 1 every 4 hours thereafter until symptoms were relieved or until 5 tablets were taken. Those persons given benadryl were told to take 2 capsules immediately and then 1 capsule every 4 hours. All were told to return when both objective and subjective symptoms subsided, and the patient's word was used as the index of the effectiveness of the medications. Two days was set as the time limit in which drugs were credited as being of value because in that time 40 per cent of those persons under study were symptom free and required no medication. One thousand two hundred cases of motion sickness were observed in this phase of the investigation.

"The prophylaxis of motion sickness was attempted by issuing medication for the passenger, with typewritten instructions to take 1 capsule 30 minutes before sailing time and then 1 every 4 hours until the 5 units of medication given each passenger were consumed. These instructions were repeated verbally to an assembly of all passengers with the added request that they report to sick bay if any illness developed. One thousand six hundred persons were observed in this phase of the study."

Therapeutic Effectiveness.—Those persons to whom no medication was given remained ill for the first 24 hours; by the end of 48 hours about 40 per cent had recovered.

"When a placebo (lactose) was given, 14 per cent of the persons reported they had recovered at the end of 30 minutes and 46 per cent reported themselves cured in 4 hours when the second placebo was given.

"Army Motion Sickness Preventive produced alleviation of symptoms in 17 per cent at the end of 30 minutes and maintained a slow but steady rise until, at the end of the second day, 71 per cent of the persons receiving the drug reported themselves to be symptom free.

"Forty per cent of those persons receiving 100 mg. benadryl stated that they were 'cured' in 30 minutes whereas, at the end of 60 minutes, 82 per cent were symptom free. This increased to 88 per cent at the end of 2 hours and no higher percentage of relief was obtained throughout the 2 day period of administration of benadryl.

"Dramamine gave relief in 58 per cent of motion sickness cases in the first 30 minutes, 76 per cent in 60 minutes, and 91 per cent in 2 hours. The figure of 91 per cent was not exceeded during the 2 days of medication."

Prophylactic Effectiveness.—When no medication was given prior to or immediately after sailing, 32.1 per cent of the passengers had symptoms of motion sickness. "When placebos were given, 27 per cent had objective signs of seasickness. With M. S. P. only 17.8 per cent became seasick. When benadryl was given as a prophylactic 9.7 per cent had motion sick-

ness. Dramamine protected all but 8.1 per cent from motion sickness."

"The 29 per cent of persons who had not improved after 2 days of M. S. P. were given either benadryl or dramamine with complete relief of symptoms in a few hours in the majority of cases.

"Benadryl proved more effective than dramamine in the period from 45 to 90 minutes after administration but was surpassed at that point and remained 3 per cent less effective throughout the remaining time."

"Rectal administration of dramamine was deemed necessary in only 1 case, a woman 5½ months pregnant who could not retain anything taken orally. A retention enema of plain water with 100 mg. dramamine gave relief in 70 minutes and the patient was continued on oral therapy. In most cases, immediate repetition of the medication after vomiting was sufficient to control the motion sickness.

"In addition to the treatment of the usual cases of motion sickness, 7 women, all of whom were less than 5 months pregnant reported to sick bay with a history of vomiting several times daily before coming aboard ship and the condition had persisted. Two of the women had been receiving injections of pyridoxine without complete relief, the others had not consulted a physician. Both dramamine and benadryl proved effective in 5 of the 7 cases. Either dramamine or benadryl was given until the vomiting ceased, the drug withdrawn and placebos given until the vomiting recurred, and then the other drug given in turn. One of the women responded only to dramamine and 1 did not respond to benadryl, dramamine, or pyridoxine; she was transferred to a naval medical facility at the first port. It was noted that none of the women benefited by the placebo which was substituted for the drugs without their knowledge."

"No toxic reactions were seen from M. S. P. although the literature states that hallucinations, mental cloudiness, change of heart rate, dry mouth, and cessation of sweating are all commonly found with overdosage.

"No severe toxic symptoms resulted from benadryl; however, drowsiness was noted in 58.2 per cent of a selected number of persons receiving the drug who were asked to report if they noticed any unusual effects while taking the medication. One woman complained of a severe headache which ceased when the drug was withdrawn and returned when the benadryl was again given. The headache was so severe that she preferred to be seasick rather than continue taking the benadryl which had terminated the motion sickness. This patient had the only toxic reaction, other than drowsiness, seen in over 2,000 persons who have received benadryl aboard this vessel. In very few persons was the drowsiness caused by the benadryl intense enough to interfere with shipboard duties or activities. However, with the simultaneous administration of 2.5 mg. benzedrine sulfate and 50 mg. benadryl the drowsiness was eliminated or considerably diminished, and the therapeutic efficacy unchanged."

The most common complaint against dramamine by patients was the frequent and severe drowsiness. "This finding was found in 36 per cent of the persons receiving the drug and seemed to be just as severe as that seen with benadryl although it was 22 per cent less frequent. The use of benzedrine sulfate, 2.5 mg. with each 100 mg. of dramamine, again eliminated the toxicity without diminishing its therapeutic value."

Advantages and Limitations of the Quantitative VDRL Slide Test — KIMBALL, ANNE C. AND BAUER, HENRY — *Minnesota Medicine*, 33: 573 (June) 1950.

The following summary of results is presented as an indication of the value and limitations of the quantitative VDRL slide test.

"The antigen emulsion is prepared with buffered saline and an alcoholic solution of 0.03 per cent cardiolipin and 0.9 per cent cholesterol and sufficient lecithin to give 'standard' sensitivity. . . . The major advantage is in its reproducibility.

"The qualitative tests are performed using 0.05 cc. undiluted serum and 1 drop (60 drops per 1 cc.) of antigen emulsion, and the results are read and reported as negative, weakly positive or positive. The quantitative test is done on all specimens giving a positive qualitative test on undiluted serum. Serial twofold dilutions of each specimen are prepared with saline

Specimen Number	Dilution 1:2	1:4	1:8	1:16	1:32	1:64	Report
103	W.P.*	Negative	Negative	Negative	Negative	Negative	Positive Undiluted Only
176	Positive	Positive	Positive	Positive	Positive	W.P.*	Positive Diluted 1:32
572	Positive	Positive	W.P.*	W.P.*	Negative	Negative	Positive Diluted 1:4

*Weakly Positive.

and each one is tested in the same manner as in testing undiluted serum." The highest dilution giving a positive reaction is reported in the accompanying table.

"The major advantage of such quantitation is that it measures the strength of positivity into a much higher range than the usual gradation of 1+ through 4+ on testing only undiluted serum. For example, in the accompanying table specimens No. 176 and 572 would both have been read positive 4+ by the older gradation method, but the quantitative tests show specimen 176 to be eight times more positive than specimen 572.

"During the six month period October, 1949, through March, 1950, 3,227 specimens giving a positive result on undiluted serum with the VDRL slide test have been quantitated." Sixteen hundred and forty-two of the specimens are positive only undiluted or in dilution 1:2. One can expect to find a considerable number of false positives in this group although many of these are specimens from treated cases of syphilis. In 993 of these 1,642 specimens the Kolmer-Wassermann test also showed some reaction.

In 915 specimens the VDRL tests were positive in dilutions 1:4 and 1:8. False positives will be unusual in this group. The Kolmer test showed some reaction in 785 of these 915 specimens.

In 670 specimens the VDRL was positive in dilutions 1:16 or higher. "False positives in this group will be exceedingly rare."

On retesting 100 positive specimens the same day there was exact agreement in 71 per cent. "Disagreement greater than one dilution was not encountered. Variables which contribute to the 29 per cent disagreement in results are as follows:

"1. Variation in reading by two technicians.

"2. Deviations from ideal mixing. (It is not practical to use separate pipets for each dilution.)

"3. Variation in serologic pipets.

"4. Variation in time elapsed since inactivation of the serum."

When the retesting was done one or two days later only 59 per cent gave exact agreement, 37 per cent differed by one dilution, and 4 per cent gave results differing by two dilutions. "For this group additional variables contributing to disagreement are as follows:

"1. Slight variation in the antigen emulsion prepared on different days.

"2. Effect of reinactivation on the specimens."

From 210 individuals the writers have received two specimens collected within one week. Within seven days one would seldom expect to see significant changes in titer of positivity except in progressing primary syphilis. "Exact agreement was obtained in 53.8 per cent." Differences of one dilution on two specimens cannot be considered to indicate any significant change in titer of positivity, and in a small percentage of cases even two dilutions may be due to technical variations.

"Quantitative Kahn tests and quantitative VDRL slide tests have been done on 628 specimens."

The greater sensitivity of the VDRL test as compared with the Kahn was clearly indicated. Forty-five specimens gave quantitative Kahns of 40 units. "These Kahn tests are positive in a serum dilution of 1:10. When these 45 specimens were tested by the quantitative VDRL test, 14 were positive in dilution 1:16, 18 positive in dilution 1:32, 12 in dilution 1:64, and 1 in dilution 1:128. With the 153 specimens giving negative Kahn tests the VDRL test results were negative in 76, weakly positive in 40, positive 'undiluted only' in

29, positive diluted 1:2 in 7, and positive diluted 1:4 in 1.

"Taking into consideration the technical variations in test procedure in these two methods of quantitation, the correlation of the results is good. Quantitation by both procedures adds little, if any, significant information."

"Both spinal fluid and blood specimens have been tested on 168 known cases of syphilis." These were classified into three groups according to the results on the spinal fluids: (1) Kolmer and VDRL tests both positive; (2) Kolmer or VDRL test positive; and (3) Kolmer and VDRL tests both negative. The quantitative VDRL tests on the blood serum showed an equally wide range of titer in all three groups. In group 1 with both tests positive on the spinal fluid, 24 per cent of the blood specimens were positive diluted only 1:2 or showed even weaker results. In group 2 with one test positive on the spinal fluid, 32 per cent of the bloods were positive diluted 1:2 or weaker.

"Colloidal gold curves have also been done on the majority of these specimens. In group 1 the gold curves were positive on 41 specimens (36 gave 'paretic' type curves) and negative on 20. Nine positive colloidal gold curves were on spinals from the 15 persons with low titer (1:2 or less) quantitative tests in the blood. In group 2, positive gold curves were obtained on 10 spinal fluids (8 gave 'paretic' type curves) and 15 were negative. Four of the positive gold curves were on spinals from the 13 persons with low titer (1:2 or less) quantitative tests in the blood. One specimen in group 1 and 1 in group 2 was insufficient for the gold curve. In the negative group (3) 1 positive gold curve was obtained; 48 gave negative gold curves. This test was not done on the 31 remaining specimens."

If the blood serum shows only a low titer positivity, this is no assurance that the spinal fluid will be negative, nor is a high titer suggestive that the spinal fluid will be positive. "Consequently the quantitation of positivity in blood serum is of no value in predicting the reaction in spinal fluids. Whenever indicated, spinal fluid should be examined regardless of the results on the blood."

It is concluded that quantitation has the following advantages:

"1. The higher the dilution in which the test is positive, the less is the possibility of a false positive.

"2. Changes in titer can be followed during treatment. This is most important in early syphilis."

The limitations are:

"1. Regardless of the quantitation, all positive tests should be repeated. Two full vials of blood for the 'battery of tests' are desirable on second specimens.

"2. Variations of one dilution (first specimen positive diluted 1:4, second specimen positive diluted 1:8) have no significance, since such change can be due to several technical variations in the test procedure.

"3. Strength of positivity as indicated by the dilution does not correlate with the clinical activity of the infection.

"4. Spinal fluid examination should be made whenever indicated, regardless of the quantitative result, since over 25 per cent of patients with positive spinal fluids have low titer positive reactions in the blood (positive diluted 1:2 or weaker)."

5. Approximately 6 per cent of the specimens have been insufficient for quantitation. "One full vial (6.0 to 7.0 cc.) is requested."

The Clinical Application of Quantitative Reports of Serologic Tests for Syphilis — LYNCH, FRANCIS W. — *Minnesota Medicine*, 33: 579 (June) 1950.

While certain advantages are to be gained from quantitative studies, the author wishes to warn against too great dependence upon tests and his purpose is to assist in their cautious and correct application.

"The most clearly evident limitations of quantitative tests are:

"1. Quantitative studies do not eliminate the possibility of technical or clerical errors and one must not depend on results obtained on a single specimen.

"2. Serial dilution of serum does not increase the specificity of a serologic reaction.

"3. There is no dependable relation between the amount of reagin and severity of syphilis or the need for treatment."

"The VDRL antigen has increased the specificity of serologic tests for syphilis and quantitative reporting will increase diagnostic accuracy in some cases since reactions occurring at higher dilutions are more likely to be specific than those observed only in undiluted serum. . . . In doubtful cases the VDRL report must be correlated with others since the likelihood of a false reaction is increased when there is conflict (e.g., VDRL negative, Kolmer positive, or the reverse). Variations in intensity of reaction may be reported in a series of tests at intervals of one or several weeks. While slight variations may be of no significance, greater ones suggest lack of specificity, and sustained upward trends are likely to be significant of increasing specific activity. Since time to observe the serologic trend may be of great help in diagnosis, it is fortunate that in the absence of clinical evidence or spinal fluid changes, there seldom is need for haste. The addition of quantitative study does not change the general principles that through physical examination, accurate personal and familial history, spinal fluid study, and patience are necessary for the accurate diagnosis of syphilis.

"In this series diagnostic help from quantitation was obtained in several cases. Diagnosis had long been delayed in 1 case because of numerous variable and conflicting reports, but after several years a specimen was reported as 4-plus in all tests and VDRL positive in dilution of 1:8, and later at 1:16, the higher dilutions suggesting that the progressive serologic change had been great rather than slight in degree, as might have been suspected if the VDRL test had been reported only as positive.

"In another instance a false diagnosis of syphilis may have been averted in the case of a penile lesion closely resembling a chancre. A series of tests was reported as follows:

Kline	2-plus	2-plus	4-plus
VDRL	positive	positive undiluted	positive undiluted

"Too much importance was not placed upon the 4-plus report since the VDRL reaction occurred only in low titer. Only a few days later both tests reverted to negative. (Fortunately the Kolmer reaction had remained negative throughout the period of observation.)

"In serial studies of several patients the VDRL reaction ranged from negative to positive in dilution of 1:2 in cases where other tests were reported negative to 4-plus, and no diagnosis of syphilis was made."

"Rising serologic titers must be appraised as possible evidence of early, untreated syphilis (acquired or congenital). Negative reactions occur during the first four or five weeks of infection, then follows a rather rapidly progressive rise in titer to a peak during the 'secondary stage' of the disease, after which the serologic titer decreases and within a year or two becomes fairly stable, at levels which vary greatly from patient to patient and seem to have little or no relation to the severity of the disease. Though the serologic level is not directly related to the activity of the disease, negative serologic reactions are rare in active late syphilis. Clinical evidence of previously active inflammation may or may not be accompanied by serologic activity (e.g., cutaneous or osseous scars or inactive — 'burned-out' — tabes with residual neurologic changes).

"The following examples from this series show how undependable is the titer as an indicator of activity of infection and need for treatment:

Titer	Nature of the Syphilis
1:128	old, previously treated for cutaneous gumma.
1:64	old, previously treated slightly.
1:64	old, untreated, cardiovascular syphilis.
1:32	late, active cutaneous syphilis.
1:16	late, active neurosyphilis.
1:8	late, persistent spinal fluid changes, recently retreated.
1:2	late, treated, seroresistance in spinal fluid.
undil.	active interstitial keratitis.

"Such examples clearly illustrate that quantitative reports must not be used as direct indications of the necessity for, or the character or amount of, treatment."

"The greatest advantage of quantitative serologic study is in the evaluation of results of modern, rapid, intensive therapy for early syphilis. Here one expects a rapid, progressive drop in titer to negativity in one to four months. (When treatment has been instituted before serologic reactions have become positive, or while they are still increasing in intensity, there may be a transitory rise immediately after starting

to treat—a 'serologic Herxheimer reaction.') Even when treatment has been started as early as one or two months after infection, one will observe some patients whose serologic response progresses steadily to a point just above negativity (e.g., weak positive, or positive undiluted only, or in dilution of 1:2) and then persists at that level, fluctuates slightly, or diminishes very slowly. Treatment has not failed; these patients have had adequate therapy and need not be retreated. After treatment of early syphilis the blood should be tested monthly for a year, every two or three months the second year and semiannually thereafter. The spinal fluid must be examined 6 to 12 months after completion of treatment, and abnormal changes require immediate therapeutic attention.

"In this series a serologic Herxheimer reaction was noted in a patient with late congenital syphilis with doubtful serologic reactions, given penicillin therapy because of interstitial keratitis. Before treatment, on 2 occasions the Kolmer reaction was negative and the VDRL positive undiluted only, but following treatment the Kolmer reaction was doubtful 1 plus-minus and the VDRL positive when diluted 1:2.

"In other instances the serologic reaction becomes less intense following treatment. A woman treated late in pregnancy gave birth to an infant who later developed evidence of osseous syphilis, and serologic reactions of Kline 4-plus, Kolmer 4-plus, VDRL positive in dilution of 1:2. Penicillin therapy was begun five weeks after birth and all the serologic reactions were completely negative three months later."

"After rapid intensive treatment for early syphilis seroresistance at relatively high levels is rare (e.g., dilutions of 1:8 or greater). When there is no clinical evidence of active inflammation and the spinal fluid is normal, the significance of such seroresistance is questionable. Perhaps there may be small foci of slowly progressive infection or equally possibly the high level of antigen represents a favorable degree of immunity. At any rate there is little risk if such patients are retreated after six months and then closely observed but given no therapy thereafter, unless the titer rises further.

"The greatest benefit of quantitative tests is the early demonstration of serorelapse or reinfection. Serologically, the two are indistinguishable. It must be emphasized that such setbacks are proved only when noted on two or more tests and never on a rise of serologic titer demonstrated on a single specimen. Clinically, the chancre of reinfection precedes the rise in titer while the mucocutaneous infectious relapse follows serorelapse. Frequently, it is important to distinguish the sequence and this can hardly be done without a series of tests with quantitative reports.

"Early latent syphilis may respond less rapidly as in the patient whose reactions at start of therapy were Kline 4-plus, Kolmer 4-plus, VDRL positive 1:16 and were the same one month later. At four months the Kline and Kolmer remained 4-plus, but the VDRL was positive only in 1:8 dilution, offering evidence of some favorable effect from the treatment.

"In a patient with previously treated asymptomatic neurosyphilis the giving of penicillin failed to modify a VDRL-positive reaction at 1:8 dilution. However, in clinically progressively active neurosyphilis similar treatment was followed by a change from VDRL positive at 1:16 to positive only when undiluted. (The Kolmer reaction remained 4-plus and the Kline changed from 4-plus to 3-plus.)"

The clinician must not base decisions on insignificant changes. "It must be particularly remembered, for example, that positive in 1:64 dilution does not mean 'twice as much syphilis' as in 1:32 dilution, but only that one more dilution of the serum allowed demonstration of a positive reaction which may have been due to technical error, extrinsic changes after collection of the serum, or normal and natural variation in the serum content of syphilitic reagin, without significance on the ultimate course of the disease."

"When gonorrhea and syphilis are acquired simultaneously, the former is often treated by penicillin before the latter is serologically or clinically demonstrable. The syphilitic infection may be aborted, masked or delayed in its appearance but frequently repeated serologic tests will aid in its early recognition and rising quantitative titers have obvious significance."

Homologous Serum Hepatitis—Robinson, James W., Twaddell, Donald N. and Havens, W. Paul, Jr.—*Annals of Internal Medicine*, 32: 1019 (June) 1950.

"Homologous serum hepatitis has been classified as a viral disease, transmitted by the parenteral inoculation of human blood or its products obtained from carriers of the causative virus. . . . Homologous serum hepatitis may be transmitted by the use of contaminated syringes or needles, or by the administration of convalescent human serum, vaccines containing human serum, or transfusions of plasma or blood containing hepatitis virus."

"During the five year period from 1942 to 1947, 15 cases of hepatitis presumably due to transfusions of plasma and/or blood occurred." Of these, 3 received the probably icterogenic material in other hospitals; the remaining 12 received blood and/or plasma at the writers' hospital. "During this time, there were in the hospital 454 beds, with an annual admission rate (1946) of 9,896, and an average daily census of 322 patients. Of the 15 cases presented, none occurred in 1942, 1 in 1943, 3 in 1944, 2 in 1945, 4 in 1946, and 5 in the first seven months of 1947.

"The 15 patients ranged from 21 to 70 years in age, with an average of 52 years. . . . The group included 10 males and 5 females. Thirteen patients were white and 2 were colored, the latter, both females.

"The majority of patients (11) received blood and/or plasma in relation to surgical procedures. Four medical patients were included in the group. The incubation period for each patient was calculated from the date of administration of plasma and/or blood to the recognition of jaundice. When more than one transfusion was given, minimum and maximum incubation periods were determined for both blood and plasma. For blood, the minimum and maximum possible incubation periods ranged from 28 to 117 days. For plasma, the minimum and maximum possible incubation periods ranged from 28 to 145 days.

"In certain cases, the exact date of appearance of jaundice was not known and, in addition, certain patients were discharged from the hospital with slight icterus, so that the exact date of disappearance of jaundice was not determined. However, the figures available indicate that the duration of jaundice ranged from a minimum of 11 days to at least 80 days, with a roughly estimated average of 25 days. In some instances, jaundice was not the first symptom but was noted 7 to 10 days following nausea, epigastric discomfort, or low grade fever. In most cases, the course was benign and improvement rapid, but death occurred in 3 patients, giving a mortality rate of 20 per cent for this small group. The duration of jaundice in those who died was, in general, shorter (11, 13 and 28 days, respectively), and the course more fulminant."

"Of the 15 cases, 8 received plasma alone, 6 both plasma and blood, and 1 received blood alone. Thus, pooled plasma, the more likely carrier of hepatitis virus, was received by 14 of the patients. . . . The statistical importance of multiple donors to pools of plasma in increasing the chance of contaminating any given pool has been emphasized.

"Attempts were made to investigate each pool of plasma and/or transfusion of blood received by the 15 patients who developed acute hepatitis. Efforts were made to determine the presence of hepatitis among the donors to the incriminated pools, as well as the incidence of hepatitis among other recipients of the same pools, but follow-up studies were disappointing. A large number of the donors were seamen, military personnel, or transient residents of the community during the war years, rendering contact with them virtually impossible."

"Before 1946, the data concerned with donors and recipients were not complete." However, in the 19 month period from January 1946 to August 9, 1947, it was possible to determine in some degree the incidence of hepatitis with jaundice following transfusions of plasma and/or whole blood given at the writers' hospital. "During this period, 64 pools of plasma were made from the blood of 1,143 donors, with a range of 9 to 22 donors per pool. This plasma was given to 621 recipients of whom 6 developed acute hepatitis after an appropriate incubation period. Two of these patients also received whole blood. The possibility that these 2 patients were

infected by blood rather than plasma must be considered, but the likelihood of this is not great in view of the known greater infectivity of plasma." In further support of this is the fact that the plasma received by one of them was from a pool which produced hepatitis in another patient. "During this same period, 1,635 patients received one or more transfusions of citrated blood from 4,294 donors. Only 1 patient who received blood alone developed homologous serum hepatitis. Although the incidence of disease is apparently low (0.96 per cent after pooled plasma, and 0.06 per cent after blood), the incompleteness of follow-up, in addition to the difficulty in the diagnosis of subicteric hepatitis, makes possible the concept that the actual incidence of disease may have been greater.

"Of particular importance, however, is the fact that, although the incidence of hepatitis was apparently low, the percentage of potentially icterogenic pools of plasma was high. The 6 patients who developed hepatitis had received 10 different pools of plasma. Two patients received the same pool, emphasizing its probable icterogenic capacity; 3 patients received two different pools each; and 1 patient received three pools." Thus, if all pools were contaminated, the incidence of infected pools of plasma during this period would have been 10 out of 64. If only a single pool given to each recipient was contaminated, the incidence would be 5 out of 64.

Treatment of Typhoid Fever with Chloromycetin — ONETTO, R. AND CHAPARRO, G. — *Revista medica de Valparaiso*, 3: 110 (May) 1950.

In the last 10 years so much progress has been made in the acquisition and application of bacteriostatics that, since the discovery of the sulfa drugs, a complete revolution of infectious diseases has taken place. These new drugs have also affected the clinical and prognostic evolution of these infections. That tubercular meningitis has been cured with streptomycin is sufficient proof of the foregoing statement.

Chloromycetin, one of the new bacteriostatics, has qualities which assure therapeutic results. These qualities are: low or no toxicity in clinical doses; its field of antibacterial action is sufficiently wide and effective; its convenience of administration—almost exclusively oral and the preparation of the product synthetically, which has identical activity to that of the original.

Chloromycetin is derived from the Streptomyces. Others in the same group are estreptomycin, aureomycin and neomycin.

It is a bitter-tasting white crystallized powder, being slightly soluble in water; it comes in capsules of 0.25 Gm. for oral use. Although it has been used intravenously, most authorities prefer oral administration. It is rapidly absorbed and at the end of 2 hours is diffused through practically the whole organism, reaching the highest levels in the blood stream 2 and 6 hours after administration; progressively diminishing thereafter until between 8 and 22 hours it is no longer detectable in the blood stream.

In vitro experiments confirm that chloromycetin would be effective in rickettsiosis and in the following: Aerobacter, Brucella, Corynebacterium, Diplococcus, Escherichia, Hemophilus, Klebsiella, Micrococcus, Neisseria, Pasteurella, Proteus, Pseudomonas, Salmonella, Sarcina, Shigella, Streptococcus and Vibrio.

Clinically, it has been used with good results in gonorrohea, active brucellosis, bacterial pneumonia, epidemic typhus, (tsutsugamushi) and typhoid. Clinical observations revealed that chloromycetin was far superior to aureomycin in the treatment of typhoid.

In 5 cases of typhoid complicated with encephalitis and 3 cases of common typhoid, with doses varying from 1, 5 and 6 Gm. daily, only 1 patient in the first group died from a relapse and intestinal perforation.

Of 11 clinical cases observed by the authors 8 were males and 3 were females; their ages ranged from 9 to 41 years. Nine of them had typhoid fever, 1 paratyphus A and another paratyphus B. In all these cases the diagnosis was confirmed clinically and bacteriologically by means of blood cultures. Nine of the cases were positive for *Eberthella typhosa*; 1, paratyphus B, was negative. In the paratyphus A case, diagnosis was arrived at exclusively by agglutination test and the clinical picture.

Of the whole group, 4 cases at the beginning of therapy were in a general grave

condition with dulness of the sensoriums; there was delirium and psychomotor excitation, 1 case having symptoms of encephalitis.

The doses used were consistently: one attack dose of 3 Gm., in a period of one hour to an hour and a half, which was followed by doses of ½ Gm. every three hours until the temperature had fallen, except in 1 case in which ½ Gm. was given every two hours. Later the doses were progressively reduced, giving in 9 cases a total dosage of 30 Gm. and in another, due to encephalitis, 39 Gm. were given before recovery was obtained.

In 6 cases the temperature dropped on the fourth day after the beginning of treatment, in 4 cases, on the third day, and in the 1 case of paratyphus it was broken on the eighth day.

There was not a case of perforation in the entire group.

In the group, 8 cases were treated only with chloromycetin; in 3, treatment was started with sulfathiazole, 6 Gm. daily and penicillin 800,000 units daily without obtaining favorable results. Treatment was changed to chloromycetin with the results already set forth. At the end of the treatment there were no positive cultures. The agglutination tests showed no rise in titer.

Treatment of Creeping Eruption with Hetrazan. Report of 13 Cases — Horton, Samuel H., Jr. — *United States Armed Forces Medical Journal*, 1: 668 (June) 1950.

"Creeping eruption is a term applied to a number of diseases of the skin characterized by tortuous migratory lesions produced by the burrowing of larvae."

Since June 28, 1949, 21 cases of creeping eruption have been seen by the writer. "The youngest patient was 18 months of age and the oldest, 49 years. There were 10 males and 11 females. The number of active larvae varied from 2 to an estimated 25. The most common site of infection was the foot, particularly around the toes, and these patients were often referred with a tentative diagnosis of epidermophytosis. The buttocks and genitals were often involved; the hands, back, and legs, rarely. All patients or parents could give a definite time of infection, usually immediately following a picnic, beach party, wading in ponds, playing in sand piles, or working in the yard. The latent period from the initial penetration of the skin by the larvae until symptoms appeared was usually less than 48 hours and often in a few hours. Most patients thought they had been bitten by mosquitoes, sand fleas or ants since small discrete papules were initially evident. In a few days the migrations of the larvae were plainly visible. The intense pruritus was usually worse at night. The patients slept fitfully, often clawing the offending areas viciously. Children cried out in their sleep and awoke sobbing and scratching. Patients have been known to mutilate their bodies with penknives and needles in a fruitless effort to rid themselves of the burning pruritus."

"Of the 21 patients with creeping eruption, 7 were transients who could not be seen regularly and were treated with ethyl chloride spray. Due to a temporary shortage of the drug one had combined therapy. Thirteen were treated with hetrazan (diethylcarbamazine) alone. These patients were weighed carefully and the dose computed on 2 mg. per Kg. body weight three times daily before meals. Children and adults received the same relative dose. Initial roentgenograms of the chest were taken because Löffler's syndrome has been reported with creeping eruption. Follow-up roentgenograms were taken in instances where there were significant complaints of a dry hacking cough. Only 1 case of Löffler's syndrome was noted. Complete blood counts and urinalyses were done twice weekly and each patient was instructed to report any nausea, vomiting, cramps, diarrhea, or general malaise. Not a single untoward reaction was reported with the dose employed. Several facts are worthy of note. The pruritus usually became minimal in 48 to 72 hours. If the patient forgot to take the drug or was temporarily without it the pruritus usually returned. The number of active larvae, as measured by their activity, gradually decreased rather than all ceasing at the same time. The average time required to acquire clinical cure was about 3 weeks although 1 patient required only 8 days; another re-

quired 30 days, but after the first week there was little complaint. Perhaps a higher dosage would effect a more rapid cure. One patient was apparently well in 9 days but noted larval activity 1 week later. He was retreated, employing the same dose, and a permanent cure was effected 17 days later."

"Of the 13 patients with creeping eruption who were treated only with hetrazan, 9 were clinically cured. Two failed to return for their final check-up but since both were progressing satisfactorily when last seen it might be assumed that they were cured and saw no need to make an unnecessary trip to the hospital. However, these 2 are included in the 4 failures."

Herpes Zoster Treated with Chloromycetin — St. John, Byron D. — *New York State Journal of Medicine*, 50: 1112 (May 1) 1950.

"Four cases of herpes zoster are presented that were apparently greatly helped, if not aborted, by the use of chloromycetin. The 24 hour dose was 50 mg. per Kg. of body weight." It is the writer's impression that the dosage used was excessive.

"Case 1.—This 54 year old man developed pain between the shoulder blades on May 14, 1949, which became very severe and required aspirin, codeine, and an electric pad for relief. Four days later, on May 18, a patch of vesicles, 2½ cm. in diameter, was discovered over the fourth dorsal vertebra in the midline with two tiny patches of vesicles appearing along the course of the fourth dorsal nerve on the right.

"The patient was started on 50 mg. of chloromycetin per Kg. of body weight every 24 hours. In this particular patient, who weighed 200 pounds, the dosage was four capsules every six hours around the clock. Each capsule contained 250 mg. of chloromycetin. He received 32 capsules in the first 48 hours; the dosage was then reduced to four capsules every 8 hours around the clock, and at the end of 72 hours the dose was two capsules every 12 hours until the total of 48 capsules was taken. There was complete relief of pain after 36 hours of medication with only a vague itching sensation remaining. No new vesicles developed. It took six weeks for the crusts to disappear from the involved areas.

"Case 2.—This 45 year old man developed pain over the lower rib on the right side in the axillary line on May 30, 1949. On June 2, four days later, the diagnosis of herpes zoster was made. This patient had an extensive vesicular lesion along the course of the seventh rib on the right. The pain was excruciating. He was put on the same dosage of chloromycetin as case 1 with a little more sedation. At the end of 36 hours the pain was greatly relieved, and the rash had stopped spreading. By the end of 48 hours he was free of pain. This patient weighed 145 pounds and took 36 capsules for his entire treatment.

"Case 3.—This was a 50 year old man weighing 200 pounds. He first felt pain in the left chest posteriorly on June 2, 1949. It became steadily more severe, and a crop of vesicles broke out on June 9. The pain steadily became worse and was not relieved by sedation." The writer first saw him on June 12 and started him on chloromycetin, 50 mg. per Kg. of body weight in each 24 hours, which equaled four capsules every 6 hours for two days. "The dose was then reduced to two capsules every 6 hours for 48 hours, making a total of 48 capsules.

"The rash was very extensive, reaching from the vertebral column around to the midline anteriorly and varied from 3 to 7 cm. in breadth. It was spreading at the time treatment was started. At the end of 36 hours the pain was greatly relieved, and the rash spread no further. At the end of 48 hours the pain was gone. However, in this patient the pain recurred spasmodically, and on June 22, six days after treatment was stopped, the patient had a severe spasm of pain which lasted a few hours with no spread of the vesicles."

Case 4.—This case was a 74 year old woman. "This patient weighed 160 pounds and had a vesicular rash with pain diagnosed as herpes zoster. She was given a loading dose of six capsules of chloromycetin, 1½ Gm., and two capsules every six hours for three days for a total of 30 capsules or 7½ Gm. On the third day her pain had stopped, and there was no further

spread of the rash. She has remained free of her symptoms."

"It is gratifying to see this stubborn pathologic entity apparently overcome quickly and thoroughly by a relatively nontoxic oral medication."

Aureomycin and Amoebic Dysentery—ARMSTRONG, T. G., WILMOT, A. J. AND ELSDON-DEW, R.—*Lancet*, 2: 10 (July 1) 1950.

The authors record below their results with aureomycin in a standard series of 52 African cases of acute amoebic dysentery, 5 African cases of exceptional severity, and 4 milder European cases.

"Material and Method.—In Durban and its environs many thousands of native Africans live in overcrowded shacks without any form of sanitation. Amoebic dysentery is endemic and over 2,500 cases a year are admitted to this hospital alone. The form of the disease is acute and serious with severe colonic ulceration and myriads of trophozoites in the stools. In 1946 the case mortality rate was 4.5 per cent. The disease, therefore, produces large numbers of patients who may be regarded as a uniform population on which the various therapeutic agents may be tested on a large scale.

"For therapeutic trials some selection of patients was necessary. For domestic reasons only males were used. All patients were complaining of diarrhoea with blood and mucus, showed ulceration at sigmoidoscopy, and had actively motile amoebas in stools or scrapings." The attack was the first in all but 6 of the 52 cases, and in these 6 the original attack had occurred more than 12 months before the authors saw them. "Cyst-passers were not accepted for the series. Cases showing chloride deficiency, abdominal distention, sloughs on sigmoidoscopy, or signs which have been found to presage perforation or ileus, were excluded because it was thought unjustifiable to experiment on such severely ill patients.

"Sigmoidoscopy was done daily until all ulcers had healed, and on the tenth, fifteenth, twentieth, and twenty-seventh days when stool examination was also carried out both by direct and zinc sulphate flotation methods. When possible, scrapings from ulcers were examined for parasites. Results were classified into three categories:

Success: Symptom free. All ulcers healed and no amoebas found in stool examination.

Possible Failure: Usually symptom free. One or more ulcers still open, but amoebas not found in stools or scrapings.

Absolute Failure: Open ulcers still present and motile amoebas still demonstrable.

"Follow-up was attempted at monthly intervals after the completion of treatment; but, in spite of the offer of payment to those Africans who returned, the results were very incomplete.

"Dosage.—Aureomycin was given by mouth in doses of 0.25 Gm. four times daily at 6 hourly intervals for 15 days. No other active drug was given, but from the fifteenth day onwards a placebo of calcium gluconate 5 grains three times daily was given by mouth.

"Results.—Of the 52 patients, 1 who was apparently cured at 15 days refused further observation and discharged himself. He is accepted as a success at 20 days but is discarded from the series at 27 days, because he cannot be assumed to have remained well. One patient, an absolute failure at 20 days, was removed from the series and given emetine and 'Diodoquin.' He is included in the figures at 27 days because he may reasonably be considered to have remained a failure on this date." Thus, after 27 days of treatment, 48 patients were classified as a success, 2 patients as possible failures and 1 patient as an absolute failure.

"Daily sigmoidoscopy showed a remarkably rapid rate of healing. Twelve cases were completely healed by the fourth day, and at the end of 7 days no less than 29 were healed. Before treatment, ulcers were nearly always covered with mucopurulent exudate; but this soon cleared. Healing usually began at the periphery of the ulcers, but sometimes the whole surface of the ulcer appeared to acquire epithelium simultaneously in a matter of a few days. One of the striking effects of aureomycin was the normal appearance of the mucosa between the ulcers. In these acute cases the mucosa between the ulcers is usually inflamed and oedematous, and with ordi-

nary amoebicidal drugs it takes several weeks to return to normal; with aureomycin the return to normality occurs in a few days.

"Clinical improvement preceded healing by several days, and diarrhoea ceased usually after one to two days. No toxic side effects were noted; but the African is notoriously reticent about minor complaints.

"Disappearance of amoebas was equally rapid and dramatic. Daily examination of exudate obtained at sigmoidoscopy failed to reveal amoebas in 6 cases on the second day, in 12 cases on the third day, and 19 cases on the fourth day. By the fourth day, therefore, 37 out of 51 cases had been cleared of amoebas. By the ninth day all cases were free of amoebas, with the single exception of the patient who was an absolute failure throughout. It was found in most cases that on the third or fourth day the amoebas greatly increased in size, sometimes reaching a length of 90 μ. It seemed almost as though their powers of division had been destroyed, for they usually vanished a day after the appearance of these 'giant' forms. The 2 cases classified as 'possible failure' were symptom free."

Follow-up, owing to the lack of cooperation of the patients, has been very incomplete, and full reports are not yet to hand. "However, those available, paint a somewhat disappointing picture." One month after discharge 27 of the successful patients returned. "Twenty were well, free of amoebas, and without ulceration at sigmoidoscopy. But the other 7 came because they were sick, and all these were found to have ulcerated colons and large numbers of trophozoites in their scrapings. One quickly died from fulminating amoebiasis and clinical diphtheria. Three of these relapses occurred within two weeks of discharge, 2 within three weeks, and 2 at four weeks. One patient had a hepatitis, and all, apart from the one who died, responded to emetine and diodoquin.

"Seven 'follow-ups' are available at two months, 2 at three months, and 1 at four months. All show normal bowels and negative stools." So far the authors have seen no relapses after the end of the first month from discharge.

"Five Severe African Cases.—These patients were considered too ill to be included in the experimental series. This type of case had never before been accepted for an experimental series, because of the risk to life involved in not using a proved amoebicidal drug."

"Three patients were found at sigmoidoscopy to have very large ulcers covered with a thick tenacious slough resembling the later stages of an ulcerated skin carbuncle. Two of these patients were dehydrated. In 1, the urinary chlorides were only 2.0 Gm. per liter. Treatment was the same as for the main series, but intravenous drips were given when necessary. One of these patients was free of amoebas on the third day, another on the fifth day, and the third on the seventh day. In 1 case all ulcers were healed on the seventeenth day, and follow-up a month after discharge showed the patient to be well, without ulceration of the colon. The second patient had open ulcers with exudate on the twentieth day, though much healing had taken place and no amoebas could be found. He was given emetine and diodoquin on the twentieth day, and was healed by the thirty-fourth day. The third showed only slight improvement after seven days of aureomycin although again no amoebas could be found. Emetine was added to aureomycin and he made a slow recovery. Ulcers were still open on the thirty-seventh day; but on the fifty-fifth day these were found to have recently healed.

"In a fourth patient the whole rectum was seen at sigmoidoscopy to be covered with a tenacious greenish black and gray slough, which was later passed as a necrotic tubular cast of the bowel. Aureomycin cleared this patient of amoebas and left a clear granular surface on which a stricture subsequently developed. Emetine and diodoquin were given after the twentieth day, but it was many weeks before the bowel was healed." The results in these grave cases were most encouraging.

"One fulminating case of amoebic dysentery was treated with aureomycin in larger doses — 4,250 mg. capsules in 4 hours, 10 capsules in 20 hours, and 6 in the next 24 hours. The patient had been ill for three weeks and was admitted gravely ill, with bloody diarrhoea, distention of the belly, a blood pressure of 90/75, dehydration, and a urinary chloride level of 1 Gm. per liter. Trophozoites were found

in the stools. He was given 5.5 liters of normal saline intravenously in three hours and rallied. Next day he was well hydrated, but he suddenly grew worse and died. Necropsy showed a friable congested large bowel with almost continuous white exudate and sloughs from caecum to rectum. No perforations were found.

"European Cases.—A European business man of 42 gave a fortnight's history of bloody diarrhoea. Sigmoidoscopy showed many superficial ulcers covered with exudate containing great numbers of amoebas. All ulcers were healed on the sixth day of aureomycin treatment. On the third day, giant amoebas were seen and from the fifth day onwards no amoebas could be obtained from bowel scrapings. After six weeks he wrote that he was well, but his stools have not yet been reexamined.

"A European child of 11 complained only of lassitude and headaches. Trophozoites were found in her stools. Sigmoidoscopy was normal. On aureomycin, amoebas disappeared from the stools on the fifth day. Follow-up with zinc sulphate flotation technique was negative two months later. Her symptoms were relieved within two weeks.

"Two other patients, 1 a baby of 10 months, were successfully cleared of trophozoites, and follow-up at one month was negative." Unfortunately the authors have no information on the effects of the drug in cyst-passers.

Comparison of Aureomycin and Other Forms of Treatment.—Aureomycin has been much the most successful single therapeutic agent, and the results of treatment with the standard amoebicidal drugs fall far short of it. "The only comparable effects were obtained with a combined treatment of penicillin, succinylsulphathiazole, emetine, and diodoquin."

Results show that aureomycin, when used alone, is capable of producing a very high cure-rate at 20 days. "In addition, by the ninth day of treatment, 98 per cent of the patients had been cleared of amoebas. . . . Successes with emetine are 50 per cent and with aureomycin 94 per cent. Absolute failures with emetine are 28 per cent and with aureomycin 2 per cent.

"Comment has been made on the rapidity with which the ulcers healed." Though this is the first series in which the authors have watched the ulcers daily, they feel that the rapidity of healing with aureomycin is much greater than with any other drug they have used.

The authors' experience with their small number of "follow-ups" has been a great disappointment; for 14 per cent of the successful cases have relapsed in the first four weeks after discharge. The relapse-rate is higher with aureomycin than with other drugs used in the past. "Though these early returning cases are classed as relapses, it must be borne in mind that these patients may possibly be peculiarly liable to reinfection, by virtue of their disturbed bacterial flora. In the circumstances to which they return after leaving hospital, reinfection is extremely likely. Recrudescence, however, remains the most likely explanation."

"The high relapse-rate clearly shows that aureomycin should not be used alone but should be combined with one of the hitherto accepted amoebicides." With aureomycin the dosage of emetine or emetine-bismuth-iodide could be drastically reduced, association of diodoquin with aureomycin would probably reduce the relapse-rate satisfactorily. "The great potency of aureomycin suggests its use as the drug of selection in acute ulcerative amoebiasis, and, though other agents must be used as well, its advent has brought closer the day of ambulant treatment for this disease."

Pediatrics

Essential Lymphocytophthisis. A New Syndrome of Pathology of Infancy — GLANZMANN, EDUARD AND RINIKER, PAUL — *Annales paediatrici*, 175: 1 (July-August) 1950.

Certain infectious diseases are characterized by absolute or relative lymphocytosis and if the lymphatic system is strained beyond its physiologic capacity a change to lymphopenia may supervene; diseases characterized by lymphocytosis usually show an unfavorable course if the lymphatic reaction is lacking. Certain severe infections sometimes show a more or less sudden diminution of the absolute number of lymphocytes, and this phenomenon is also considered to signify a serious prognosis. While this lymphopenia is frequently attributable to an acute failure of the lymphatic apparatus, lymphocytophthisis will supervene more insidiously and gradually when the lymphoid tissue of lymph glands, spleen and other organs is replaced by other tissues, as in extensive tuberculosis of the lymph glands and the spleen, Hodgkin's disease, myelogenous leukemia and extensive carcinomatosis of the lymph glands. The authors observed almost complete failure of the lymphocytopoiesis with a terminal absolute number of only 49 lymphocytes per cu. mm. in a case of lympho-epithelial carcinoma of the epipharynx with extensive metastases in the lymph glands and with embolism and anemic infarctions of the spleen, involving a girl aged 15. Normally the lymphocytes amount to 7,000 per cu. mm. during the first year of life, and their number decreases to 6,000 at the age of 4 and 4,000 at the age of 12. Lymphocytophthisis and lymphocytopenia may also be caused by excessive x-ray and radium treatment. Whether the modern antibiotics exert an elective unfavorable effect on the lymphocytes is not yet known. In anaphylactic agranulocytosis, lymphopenia is said to be frequent.

The first case of total alymphocytosis first reported in 1929, involved a man aged 39, with chronic diarrhea of the character of pancreatic insufficiency, and scanty signs of stenosis of the small intestine; the patient succumbed after several months to cachexia. His blood contained no lymphocytes and autopsy revealed total atrophy of the lymph glands and the spleen. The term of alymphocytosis was coined in analogy to that of agranulocytosis, but the authors prefer the term of lymphocytophthisis.

No analogous case in children could be found by the authors in the literature. Their first case concerned an infant girl who first developed stubborn thrush at the age of 7 weeks, associated with otitis media and bronchitis. Examination on admission at the age of 4 months revealed marked dystrophy, with a weight of 3,800 Gm., as compared to a normal weight of 5,800 Gm., and a length of 54 cm. as compared to a normal length of 63 cm. The skin around the mouth was reddened and showed partly weeping impetiginous efflorescences. Lips, tongue and the entire pharynx down to the larynx and esophagus showed a thick white thrush coating; the tonsils were slightly enlarged. Aphthae or ulcerations were absent. The lymph glands at the angles of the jaw and the nuchal ones were slightly enlarged while no other lymph glands were palpable. Purulent rhinopharyngitis was present. The blood picture showed 75 per cent hemoglobin, 4.2 million erythrocytes and 6,100 leukocytes with only 15 per cent lymphocytes. The tuberculin reactions were negative. Bacteriologically the nasal smear was negative, the pharyngeal smear showed fusiform rods and Spirochaetae, the gastric contents showed moderately numerous yeast cells and thrush, and the cultures revealed yeast, coli and enterococci.

Treatment included penicillin, high doses of vitamins and borax glycerin locally. After two days the left ear began to discharge pus. The general condition improved and the infant gained weight but the thrush improved only temporarily. After a week the temperature rose to 39° C. and pneumonia supervened. Recurrent fever attacks persisted and streptomycin was tried. Paravertebral pneumonia was found in the right upper field and broncho-

pneumonic foci were found in the left lower field. The lymphocytes decreased to 13 per cent of 3,800, and later to 4 per cent of 7,800 leukocytes. A blood transfusion of 60 cc. was given. Diphtheria antitoxin was also given, both intramuscularly and locally, and the local conditions improved appreciably. Temporarily a morbilliform to urticarial rash appeared; it was no serum rash. In spite of local improvement the infant refused food, the hoarseness increased and breathing became slightly stridulous. The rash recurred; the lymphocytes amounted to 2.5 per cent of 5,500 leukocytes. Blood transfusion and intravenous drip infusion were resorted to, but the condition became worse; the syndrome was dominated by intense dyspnea without stridor, examination showed emphysema in addition to the pneumonia, pulmonary edema supervened and the infant succumbed five weeks after admission. The serologic syphilis reaction was negative and no Rickettsiae could be demonstrated in the spleen.

The second case was similar. It involved a male infant, admitted at the age of 4½ months; death supervened six weeks later. This infant had experienced whooping cough, a disease which shows absolute lymphocytosis and which is therefore capable of putting a strain on the lymphatic apparatus.

The extensive thrush with transition into thrush septicemia was dominating the syndrome in both cases, and aphonia indicated extension of the fungus into the larynx. A morbilliform septic rash appeared in the second case as well. The peripheral blood showed progressive lymphocytophthisis and there were no traces of substitution by reticulum cells (monocytes) in the first case, while the second case showed early marked lymphocytopenia which proved to be fairly stationary, and increasing substitution of monocytes and transitional cells(reticulum cells) for the lymphocytes; the granulocytes showed a marked shift to the left and numerous toxic granulations. The platelets were normal and signs of a hemorrhagic diathesis were entirely lacking. In the first case the family history showed that 1 of 5 siblings had died from a similar condition at the age of 3 months but no detailed data were available. A brother of the second patient died at the age of 4 months from pyloric stenosis, seborrheic dermatitis with eczema, pyoderma, subcutaneous abscesses, enlargement of the lymph glands and staphylococcic septicemia; there was no lymphocytophthisis in this case and intense thrush appeared only terminally. There was complete abolition of blood coagulation in this case and the platelets numbered only 18,900; the bleeding time was eight minutes. Thus in these families a pathologic gene of weakness of the hematopoietic organs seems to be present which may manifest itself as lymphocytophthisis, or as in the last-mentioned case as panmyelopathy; it seems noteworthy that terminally in essential lymphocytophthisis panmyelopathy also supervenes in the bone marrow picture; the megakaryocytes are preserved longest and thrombopenia and hemorrhagic diathesis do not appear. It seems suggestive to assume that the severe thrush in infants with essential lymphocytophthisis is only made possible by the lowering of the natural resistance on the basis of constitutional weakness of the lymphatic apparatus, but it will have to be determined whether possibly the extensive thrush mycosis may produce toxic substances which attack the lymphocytes and damage the lymphatic apparatus to such an extent that the lymphocytes disappear almost completely. Recently considerable lymphopenia has been reported frequently in bronchopulmonary mycoses, but a special constitutional predisposition seems required for development of almost complete lymphocytophthisis. Autopsy of the first case revealed necrotizing moniliasis of tongue, pharynx, larynx, esophagus, stomach and ileum, panmyelophthisis, lobular pneumonia with fungous threads in the smear, pulmonary edema, vicarious pulmonary emphysema, myocardial hemorrhages, hyperemia and hemosiderosis of the spleen, fibrous atrophy of the splenic follicles, cloudy swelling of the kidneys, peripheral fatty degeneration, cloudy swelling and septic spotting of the liver and pedatrophia. In the second case it revealed generalized atrophy of the lymphatic tissue, panmyelophthisis, necrotizing moniliasis of esophagus, lungs and ileum, lobular pneumonia, bronchiolectasic emphysema and edema of the lungs, bilateral serofibrinous pleurisy, hydropericardium,

ascites, mucosal edema of pharynx, stomach and intestine, hyperemia of the spleen, cloudy swelling and fatty degeneration of the kidneys, diffuse fatty degeneration of the liver, cerebral edema, multiple skin erythemas and pedatrophia. The pneumonia was the immediate cause of death in both cases.

The atrophy of the lymphatic tissue of intestine, lymph glands and spleen as anatomic substrate of the failure of lymphopoiesis in these cases is of special type; like in severe marantic and senile atrophy the follicles disappear completely, the medullary cords are thinned and the sinuses of the lymph glands are dilated, but while in simple atrophy the reticulum cells also usually become smaller and scantier in essential lymphocytophthisis they not only preserve their size but increase in numbers and show some mitoses. Thus the atrophy primarily concerns only Aschoff's lymphoid tissue, the so-called parenchyma, while the reticular stroma shows a variable degree of proliferation ex vacuo; however, the loss of volume is usually only defectively compensated for, and at first an increase of the connective stroma does not take place. Systematic studies will have to determine whether the selective atrophy of the lymphoid tissue is characteristic of infancy or is peculiar to the affection dealt with. In the lymph glands the marginal and medullary sinuses usually show marked enlargement so that the size of the organ may remain intact in spite of the atrophy, or there may even be some enlargement and an edematous aspect. In the spleen all follicles are involved. In the second case the reticulum fibers were still thin while the first case showed already extensive involutional phenomena; namely, transformation of the cells into fibroblasts and connective tissue cells, formation of collagenic fibers and hyaline degeneration. In the first case the follicular residue and the hyperemic inflammatorily swollen pulp contained abundant hemosiderin while no hemosiderin was found in the second case. The intestinal findings corresponded to those of chronic nutritional disturbances of the infant. The glandular and superficial epithelium was unaltered while the thin reticular stroma of the mucosa was strikingly poor in free round cells. Lymphoid tissue was completely lacking but here and there in the depth of the mucosa and inside the muscularis mucosae small foci of densely massed fusiform cells were encountered, to be interpreted as stroma residue of the atrophic lymph follicles. The ileum of the second case showed rather sharply delimited hyaline tissue plaques, covered by one layer of epithelium; these plaques might have been mistaken for scars from ulcers except for the fact that the absence of true fibrous cicatricial bands and of displacement of the adjacent structures and the localization opposite the mesenterial attachment indicated that hyaline degeneration of residue of Peyer's patches was dealt with.

Regeneration of lymphatic cells from reticulum cells could not be observed anywhere; thus at least under the special circumstances the conception that differentiated reticulum cells are no longer capable of forming lymphatic cells may be correct.

The conditioning influence of dystrophy and marasmus on thrush development is well established. However, several factors indicated a closer relation of the mycosis to the basic disease in these cases. The mycosis was extensive and was also localized in places where it is rare; furthermore it had such an intense necrotizing effect that it can hardly be admitted that the mycosis was merely dependent on the lymphocytophthisis, and the possibility cannot be ruled out that toxic substances penetrated into the lymph and blood and became generalized, the more so as the fungi frequently grew into the small vessels and even into medium-sized arteries. Systemic damage to the lymphoid tissue from fungous toxins seems feasible.

Primary pulmonary thrush, without preceding necrosis and cavity formation of other etiology, is extremely rare. In the first case atelectatic foci contained widened alveolar septums with swollen epithelioid cells which were also encountered in adjacent interlobular septums and bronchi. As in the periphery of small mycotic foci of the second case such epithelioid cells were found in a similar distribution, it seems logical to assume that in the first case, too, fresh reactions to the fungous infection were dealt with. The multiple round pulmonary foci in the second case

were of rather firm consistency, with a dry surface on section, yellowish gray, and showed histologically the typical concentric structure of pulmonary mycoses; short fragments of mycelium were demonstrable only in the periphery of these foci in very few areas. The preparation had been fixed and cultural proof of the fungus was impossible. However, the assumption of a pulmonary thrush mycosis seems justified as the necrotizing effect was demonstrable at the level of the esophagus and as it is known that the fungus grows with greater difficulty in the lungs, accounting for the scanty findings of such fungi in the lungs. Thus in all probability the thrush was aspirated into the lungs and exerted its necrotizing effect but did not grow.

Though it is rare to find thrush growing in the lungs it is more rare to find it growing in the intestine. In some areas corresponding to Peyer's patches thrush mycelium could be demonstrated. When massively swallowed fungi are capable of producing mucosal necrosis it seems feasible that at an earlier stage mild irritation was caused by the fungi; as absorptive disturbances linked to such irritations have a lymphotoxic effect, the possibility of an indirect selective damage to the lymphoid tissue from intense thrush mycosis of the upper digestive tract must be admitted. The authors attribute a greater significance to this mechanism than to a direct generalized toxic mycosis. In a case reported, mycosis was lacking but the small intestine showed extensive cicatricial alterations furnishing the anatomic substrate for chronic enteral absorptive disturbances. The intense hyaline degeneration of the mesenterial and retroperitoneal lymph glands and the splenic follicles in this case may then well be analogous to the atrophy of the intestinal follicles in dystrophic infants and to the atrophy of the lymphoid tissue in the authors' cases. The total atrophy of the enteral lymphatic tissue in the second case indicates that the first stage of the generalized atrophy of the lymphatic system was dealt with, on which the clinical syndrome of lymphocytophthisis is based. The authors stress that the bone marrow showed the picture of aplastic myelopathy in both cases; clinically agranulocytosis was not produced but the histologic picture of the bone marrow proves terminal severe damage to myelopoiesis and erythropoiesis while only the megakaryocytes were present in almost normal numbers.

Evolution of Neurologic Signs of Early Anterior Poliomyelitis — Pollock, Lewis J., Boshes, Benjamin, Finkelman, Isidore, Hiller, Frederick, Chor, Herman, Brown, Meyer, Arieff, Alex J., Liebert, Erich, Tigay, Eli L., Schiller, Maurice and Sherman, Irving C. — *American Journal of Diseases of Children*, 79: 973 (June) 1950.

"Heretofore the clinical picture of early anterior poliomyelitis has been derived from the relatively infrequent examinations of large numbers of patients. It was felt that a more accurate picture of the early stages of the disease could be obtained from frequent examinations both day and night of a small number of patients." Accordingly, 11 neurologists were rotated on tours of duty of six hours each during the day and night for 30 days in the writers' hospital. "This permitted intensive study of 30 patients."

There is no spasm in the muscles in early anterior poliomyelitis.

"In all cases of meningitis, rigidity of the neck, the direct Brudzinski sign and the Kernig sign were found to a marked degree. In early anterior poliomyelitis these signs varied in frequency and intensity. Nuchal rigidity was rather constant, appearing in 92.4 per cent of examinations, but the head might be flexed to a certain degree without resistance. The Brudzinski sign appeared in 37 per cent but could be elicited from the beginning of flexion of the head in but 4 per cent. The Kernig sign appeared in 39 per cent and was most evident in the greater degrees of extension of the leg on the thigh. Both the Kernig and the Lasègue sign, especially the latter, occurred in greater and greater frequency as time elapsed after the onset of illness, suggesting that the cause for these signs in early anterior poliomyelitis is that their elicitation produces pain.

"Severe paralysis was observed as early as 18 hours after onset. Usually weakness

appeared and increased to a peak reached between the seventy-fifth and the one hundred and fiftieth hour. Once weakness appeared, it did not progress steadily to paralysis but at times diminished, frequently to the point of normal strength, then increased again and finally might result in complete paralysis or recovery. The weakness might remain constant for numbers of hours and further progress to paralysis; it might diminish and again proceed to paralysis."

"It has been said that absence of deep reflexes is the rule. They may be normal in patients with the bulbar form of the disease. When only one leg is paralyzed, the other knee jerk may be normal, and if only the arms are paralyzed the knee jerks may at times be present but rarely exaggerated. Even if only the facial muscles are paralyzed, the knee jerks may be absent."

When muscles were destined to become severely or completely paralyzed their deep reflexes were absent in 91 per cent. "When the deep reflexes of a muscle group disappeared before the fiftieth hour after onset of illness, 41 per cent of the cases terminated in complete paralysis. If the deep reflexes disappeared in from 50 to 75 hours, 50 per cent terminated in severe paralysis; when from 75 to 100 hours, in 38 per cent; when from 100 to 125 hours, in 28 per cent. When the deep reflexes disappeared only after 125 hours, in none did weakness greater than Lovett's grade 4 develop. The earlier the deep reflexes disappear, the more likely is it that the muscle group will become paretic.

"There was found as great a fluctuation in the state of deep reflexes in relation to time as in paralysis; that is, reflexes might disappear, reappear and again disappear. When a long period of hours of continued absence of a deep reflex finally ensued, then if the continued absence began soon after the first observation that a reflex was absent complete paralysis occurred in over 60 per cent of muscles. As time lengthened for the continuous absence of deep reflexes, the strength of the muscles did not diminish to the same degree as in the cases with earlier continued loss of a reflex. When no continued loss of deep reflexes was observed, then at the end of the period of observation no paralysis ensued in over 80 per cent of muscles.

"In patients some of whose muscles became severely paralyzed while in others weakness but no residual paralysis developed, there was no loss of a deep reflex subserved by the latter muscles in 164 examinations up to 100 hours and in only 6 per cent of the 51 examinations between 100 and 130 hours. They were found absent in only 3.1 per cent of 291 examinations up to the two hundredth hour and were found increased in 57 per cent."

"When the lower extremities were destined to become severely paralyzed, the abdominal reflexes disappeared in 85 per cent of the examinations up to the one hundredth hour after onset. This early absence of the abdominal reflexes was found to be a valuable prognostic sign. They were increased in 57 per cent of examinations when no muscles were destined to become paralyzed and in 42 per cent when only the upper extremities were destined to become paralyzed.

"The plantar reflexes were absent at various times in 35 per cent of examinations of severely paralyzed lower extremities in which movement of the toes was still possible. They were brisk or increased in 25 per cent of severely paretic lower extremities, in 64.5 per cent when the lower extremities were moderately paretic and in 85 per cent when only the upper extremities were paretic.

"In the presence of an upper motor neuron lesion, there is a consistent relation in which hyperactive tendon reflexes are associated with diminished or absent superficial reflexes and a positive Babinski sign." The Babinski sign was found very infrequently in these cases, more frequently when only the upper extremities were paretic. "It was fleeting and inconstant and seemed not to be due to an upper motor neuron lesion but comparable to its presence in anoxia, anesthesia, after convulsions, etc. When in 57 per cent of examinations the deep reflexes were hyperactive, the abdominal reflexes were absent in but 3.2 per cent. When in another group the deep reflexes were hyperactive in 91 per cent of examinations the abdominals were brisk in 97 per cent. When the deep reflexes were brisk in 57 per cent of examinations, the

plantar reflexes were hyperactive in 65 per cent. These inconsistencies suggest that there was no evidence of any upper motor neuron lesions in these cases."

"Direct myotatic irritability was found to be increased predominantly in muscles of the upper extremities when they were paralyzed as compared with those of the lower extremities. It was increased in 40 per cent of 295 observations on the upper extremities and 5 per cent of 365 observations on the lower extremities when the observations were made at various times during the period of hospitalization.

"Direct myotatic irritability was found to be increased in a greater percentage of paralyzed than unparalyzed muscles of the upper extremities. Thus, of 295 observations on paralyzed muscles, in 40 per cent it was increased, whereas in 691 observations on unparalyzed muscles it was increased in 17 per cent. Nevertheless, in many instances when a muscle was completely paralyzed, for example, from the one hundred and twentieth to the two hundred and seventieth hour after onset, direct myotatic irritability may not have been increased. In general, the increase of direct myotatic irritability was more related to the time after onset than to the degree of paralysis. It seemed to be increased when paralysis occurred soon after onset, whereas, despite complete paralysis of a muscle after, for example, the one hundred and sixtieth hour after onset, it may not have been found to be increased. On the other hand, in some it was increased many hours after a muscle became completely paralyzed.

"In general, myotatic irritability decreased after longer periods, so that after the two hundred and fiftieth hour no increase was found in either paralyzed or unparalyzed muscle, although the numbers of observations at this late time were smaller than in the preceding hours.

"Increased direct myotatic irritability not only was inconstant in appearance but fluctuated to a great degree in the successive observations on each patient during the time of hospitalization. This may be illustrated from an analysis of all of the cases. Between 40 and 50 hours, direct myotatic irritability was increased in 100 per cent of the muscles examined, between the one hundred and ninetieth and two hundred and tenth hours it was increased in none and between the two hundred and thirtieth and two hundred and fortieth hours it was again found to be increased in 100 per cent. The failure to find a constant correlation between the development of paralysis and other signs of denervation in the muscles was reflected also by studies on the response of such muscles to electric stimuli. Despite complete paralysis, the rheobase did not fall to the small values observed in injuries of peripheral nerves nor did the galvanic tetanus ratio fall to 1.0. In this respect, the paralysis in anterior poliomyelitis acted much as did that due to injuries of the cauda equina or brachial plexus in which sufficient numbers of nerves reached the muscle to neurotize it to such a degree that evidence of complete denervation could not be obtained and still the total number of intact fibers was insufficient to produce the energy necessary for voluntary motion."

Guiding Rules for the Treatment of Poliomyelitic Paralysis in Practice—Monrad-Krohn, G. H.—*Deutsche medizinische Wochenschrift*, 75: 918 (July 14) 1950.

During the preparalytic stage of poliomyelitis rest, preferably complete bed rest, is extremely important, as it has been shown that the paralysis becomes much worse with motor activity during the preparalytic stage. During the poliomyelitis season, therefore, every child or young adult with fever should be kept in bed and examined carefully daily for nuchal rigidity and paralysis. Bed rest is of course indicated once a paralysis has appeared, even if only the upper limbs are involved.

During the first stage, avoidance of joint complications is the main goal; the joints are endangered by contractions and by overstretching of their ligamentous apparatus with resulting abnormal mobility. In small children the danger of flexion contracture of the hip and knee joints is particularly important, and therefore in paralysis of the extensor muscles of the lower limbs the legs should be cautiously extended passively several times daily, and the children should be made to lie on their stomach for some time daily, with com-

pletely extended but not hyperextended legs; the feet should extend beyond the end of the bed in order to prevent a talipes equinus formation. The danger of the latter exists in all cases in which the extensor muscles of the foot are involved and an appropriate position of the feet is of the greatest importance and easy to obtain. Adults are simply told to place their feet against a box placed into the bed, so that the ankle joint is at a right angle and the paralyzed muscles of the anterior tibial group are protected from overstretching. Furthermore the feet must be passively moved every day in order to prevent contractures even in the rectangular position, but extensive plantar movements should be avoided so that the paralyzed extensor muscles are not overstretched. In children the rectangular position may be maintained with a plaster cast but it must be detachable so that passive movements are afforded. Once the acute stage of the disease has passed, active treatment of the paralysis may be started. About 150 muscle fibers are supplied from each anterior horn cell of the spinal cord. Fortunately only rarely all cells supplying a muscle or a synergetic muscle group are irreversibly involved and therefore usually the paralysis will be partial. Thus almost every muscle will include three elements; namely, fibers supplied by destroyed nerve cells and therefore permanently paralytic and destined for unavoidable atrophy, fibers corresponding to temporarily affected anterior horn cells and therefore only temporarily paralyzed and normal fibers. The latter are susceptible to exercise and resulting hypertrophy from the beginning, and the temporarily paralyzed ones become susceptible in due course. Active training and the resulting hypertrophy of these elements are the main factors in the treatment of the poliomyelitic paralysis. It seems probable that cautious exercise has a favorable effect on the medullary regenerative processes as well.

Thus active gymnastic treatment of poliomyelitic paralyses is analogous to training in sports. Paralyzed muscles are highly sensitive to certain factors, e.g., overstretching, and regeneration will be much faster if overstretching is guarded against; relaxed muscles have the best chance of rapid regeneration. Therefore an abduction splint is useful in paralysis of the deltoid muscle which is very easily overstretched. The paralyzed muscles must be protected against overexertion and maximal efforts should never be used; the fact should not be neglected that maximal efforts in paretic muscles are much smaller than those in normal muscles. The patients should be warned against incessant exercising all day long, and the exercises of each paretic muscle group should be carried out in a series of 10 to 12 exercises. Exercises under water are very suitable and almost indispensable for leg exercises; the patient is told to contract the paretic muscles 10 to 12 times, and often the plane of movements will have to be changed as movements may be possible in one plane and impossible in another.

Mild massage is often indicated in the presence of cyanosis and edema of the paretic limb but deep intense massage of paretic muscles is contraindicated as it may lead to overstretching of the muscle fibers. Electrotherapy is of secondary importance as compared to active exercise, and may be dangerous in the hands of the unexperienced; protracted faradic stimulation of the paretic muscle may be harmful, and interrupted faradic and galvanic stimulation may be useful, but should be left to the specialist.

The patient should be permitted to get up and walk as soon as this can be done without harm. Walking may be particularly harmful to the joints; it has not been sufficiently stressed in the author's opinion, that under normal conditions, capsule and ligaments of the joints receive an important protection by the muscles. When the latter are paralyzed ligaments and capsule cannot withstand the strain permanently, overstretching will result and the joint will become inferior from the mechanical point of view.

Thus the patient may be able to walk with a hyperextended knee in the presence of paralysis of the extensor and flexor muscles of the knee joint, but soon, overstretching of the ligaments and progressive abnormal mobility of the knee joint will supervene; that is, an avoidable articular complication will have been added to the unavoidable paralysis. As long as the muscles are still markedly paretic the patient should wear a light splint which fixes

the knee in slight flexion on walking; the splint must be detachable so that exercises can be continued.

In paralysis of the anterior tibial muscle group, the foot will descend into a talipes equinus position with each step and this will result in overstretching of the ligaments and also harmful overstretching of the paretic muscles; this harm can readily be prevented by means of an elastic bandage extending from the dorsal joint surface to the knee. Thus patients should be permitted to be up and around as early as possible, but not without thorough neurologic examination and supports corresponding to the results of this examination. The latter must be repeated at regular intervals and the supports should not be used longer than necessary. Throughout the period of treatment accurate neurologic examination furnishes the guiding rules.

Even in extensive and almost complete paralysis of the legs, walking may be made possible by training in unilateral raising of the pelvis and in rotation of the pelvis and spine, even when the legs themselves have to be immobilized in fixed supportive bandages. Although walking will be stiff and slow the patients will be extremely thankful for being able to be out of bed.

Contrary to the textbook claims, that improvement may supervene until one year after onset of the paralysis, the author states that many patients in whom exercise of still contractile muscle residue has been neglected may still be amenable to rational gymnastic treatment after a number of years.

Poliomyelitis of the Newborn. Pathologic Changes in 2 Cases — BASKIN, JOHN L., SOULE, EDWARD H. AND MILLS, STEPHEN D.—*American Journal of Diseases of Children,* 80: 10 (July) 1950.

The writers have observed 2 infants who had acute poliomyelitis in the newborn period; that is, in the first two weeks of life. They felt that a brief report of their experience with these 2 cases would be timely, as medical teaching generally has held that this disease does not occur in the newborn period because of immunity transmitted to the infant by the mother.

"Case 1.—A boy was born at 2:20 A.M. on August 11, 1949, while his mother was in a respirator critically ill with poliomyelitis of four days' duration. Outlet forceps were used to facilitate an uncomplicated vertex delivery. The obstetrician described the baby as an active normal boy, moderately asphyxiated, who responded to tracheal catheterization and insufflation and was taken to the nursery breathing normally about eight minutes after delivery.

"On arrival at the nursery, examination revealed a robust, lustily crying infant boy with frothy, saliva-like material bubbling from the mouth. The hands and feet were slightly cyanotic, but respiratory movements were good and breath sounds clear throughout both lungs. The extremities moved readily, and the reflexes were active and bilaterally equal. The neurologic examination gave negative results.

"The cyanosis cleared up completely, and the baby's course was uneventful until August 14, when a rectal temperature of 101 F. developed. There was no evidence of infection, and fever remained the only abnormality until 12:30 A.M., August 16, when listlessness and cyanosis of the lips and nail beds were noted. Significant findings were absence of response of the right foot and leg to pain and minimal response of the left. Mucus collecting in the mouth and pharynx was aspirated; oxygen therapy was started, and oral feedings were stopped. A lumbar puncture was done, and xanthochromatic fluid was obtained. The protein content of this fluid was 300 mg. per hundred cubic centimeters; the lymphocytes numbered 97 per cubic millimeter and the segmented (polymorphonuclear) leukocytes numbered 11 per cubic millimeter; an occasional erythrocyte was seen, and the value for sugar was 60 mg. per hundred cubic centimeters.

"Intracranial hemorrhage and high cord injury were considered as possible causes for the clinical picture. Medical neurologic consultants considered subdural hematoma as likely.

"Subdural taps through the anterior fontanel were carried out on August 16. No fluid could be obtained, although some clear fluid did drain from puncture sites before collodion pledgets were applied.

"The patient became rapidly worse, with extreme flaccidity, irregular respiration and progressive cyanosis, and death occurred on August 17, on the seventh day of life."

"Necropsy performed on the unembalmed body four and one-half hours after death disclosed essentially normal conditions except in the lungs and the central nervous system. Careful study of the heart did not reveal myocarditis.

"In the lungs there were regions of collapse interspersed between regions of congestion and edema. On microscopic examination foci of early pneumonitis were seen.

"In the central nervous system the leptomeninges were normal macroscopically except for congestion of the pial vessels. The falx and tentorium were normal. The brain was 60 Gm. heavier than the normal weight of 440 Gm. The convolutions were widened slightly, with commensurate narrowing of the sulci. On coronal section of the cerebrum, the white matter was moist and glistening, whereas the gray matter appeared normal. The ventricles and their ependymal lining were normal. The midbrain, medulla and cerebellum were normal. There was slight bulging of the cut surface of the cord, and the gray matter was a salmon pink without evidence of hemorrhage.

"Microscopic examination revealed the characteristic findings of acute polioencephalomyelitis, with involvement of the cord, medulla, pons, midbrain, roof nuclei and vermis of the cerebellum, thalami, hypothalamus and the cortex of both motor areas and the left insula.

"In the gray matter of the anterior horns in the cervical and lumbar enlargements, degenerative changes were evidenced by nearly complete loss of the ganglion cells and the presence of a heavy inflammatory infiltrate. Active neuronophagia was not seen, but occasionally pink-staining hyalinized remnants of ganglion cells were noted. The ganglion cells of the lateral and posterior columns revealed foci of degeneration with nests of inflammatory cells replacing them. Many of the remaining ganglion cells showed degenerative changes characterized by peripheral clumping of the Nissl substance. Sections taken from the remaining levels of the cord revealed the loss of neurons as well as the inflammatory reaction to be more focal in distribution.

"In the medulla, the motor nuclei of the cranial nerves and the inferior olivary nuclei revealed focal loss of ganglion cells with aggregates of inflammatory cells. In the lateral and medial reticular substance there was a scattered, diffuse inflammatory infiltrate.

"In the midbrain, accumulations of inflammatory foci were marked and widespread. In some instances, these foci resembled microabscesses with a preponderance of neutrophils. In other instances, sites of softening were seen with the loss of brain substance, which was replaced by swollen, vacuolated cells that resembled neutrophils and microglia which appeared to be active in phagocytosis.

"The pons exhibited rather severe involvement of the nuclei in the floor of the fourth ventricle, and to a less extent the pontile nuclei were the site of focal damage. The hypothalamus was extensively involved, whereas the thalami exhibited scattered focal involvement. The roof nuclei of the cerebellum presented rather marked loss of ganglion cells and the characteristic cellular response. Involvement of the dentate nuclei was focal.

"The reaction in the cortex was limited to both motor areas and the left insula. The cellular response tended to be limited to small foci which had replaced the ganglion cells in the midzone of the cortical cell layer.

"Perivascular cuffs of lymphocytes admixed with a few neutrophils were seen throughout the cord and the brain. This was particularly pronounced in the midbrain and the hypothalamus. Active neuronophagia by histiocytes and neutrophils was rarely seen, and only the late stage of lysis of ganglion cells could occasionally be demonstrated. Nuclear inclusion bodies were not found. Numerous ganglion cells in the less involved parts were observed to have undergone central chromatolysis with peripheral clumping of the Nissl substance.

"In general, the inflammatory infiltrate consisted of lymphocytes, neutrophils and mononuclear cells in about equal proportions. In several instances, foci were observed in which the nature of the infil-

trate was more acute, suggesting that these foci represented a more recent destruction of ganglion cells or a higher concentration of the virus. Where the softening was more marked, the acute features of the reaction were subsiding and phagocytosis of the necrotic tissue was demonstrable.

"In the cervical enlargement, where destruction of the gray matter was pronounced, the astrocytes of the adjacent white matter were swollen and were more prominent than in a control series of comparable sections from infants of the same age group. It is of interest that the infiltration in the arachnoid was moderately pronounced and that the composite cells were in approximately the same ratio as they were in the last spinal fluid examined.

"Sections from the placenta in this case were studied and no abnormality found. The placentas of 3 other women acutely ill with poliomyelitis were also found to be essentially normal."

"Case 2.—A normal boy was born November 10, 1949, after uncomplicated labor and delivery. On November 12 his mother had the onset of acute poliomyelitis, but the baby showed no signs of illness. He continued to do well, but on November 15 examination of spinal fluid obtained by lumbar puncture disclosed a lymphocyte count of 5, a segmented (polymorphonuclear) leukocyte count of 1, a protein content of 40 mg. and sugar content of 45 mg.

"There was no change until November 18, when a rectal temperature of 101 F. and listlessness were noted. The next day the extremities became flaccid, and respirations increased to 52 per minute. By November 21 flaccid quadriplegia, irregular, rapid, shallow respirations and inability to swallow had developed. Examination of the cerebrospinal fluid at that time revealed a lymphocyte count of 32, a segmented leukocyte count of 12, a protein content of 120 mg. and sugar content of 53 mg. The clinical course was rapidly downhill, with death on November 24."

"At necropsy, performed on the unembalmed body three hours after death, the abnormal findings were restricted to the heart, lungs and the central nervous system.

"In the heart no gross abnormality was noted. Histologic evidence of severe acute and healing myocarditis was found in sections taken from the ventricular septum, the left posterior papillary muscle and the lateral wall of the left ventricle. . . . Focal necrosis of muscle fibers and cellular infiltration of varying degrees were widespread, and the sites of these changes were interspersed frequently among sites of an older healing process. The foci of necrosis varied in size from that of three or four muscle fibers to that of a large number.

"In the sites of acute myocarditis, the muscle fibers were replaced by pink-staining, amorphous clumps of degenerating cytoplasm. Frequently the sarcoplasm had undergone a hyaline change. . . . There was a gradual transition from the normal tandem fibers to that of degeneration as evidenced by splitting of fibers, loss of cross striations and occasionally vacuolation of the cytoplasm. The nuclei of the muscle fibers appeared shrunken in the early stages and disappeared as the process advanced. The cellular infiltrate was moderately abundant, consisting chiefly of large mononuclear cells and to a less degree of lymphocytes and plasma cells. In some instances there was a light scattering of neutrophils.

"Interspersed among the foci of more acute degeneration were foci of healing which were characterized by myocardial stroma from which the necrotic muscle fibers had been removed. Many large mononuclear cells and a few lymphocytes and plasmacytes (plasma cells) were seen in the interstices of the stroma. Early fibroblastic proliferation was also seen.

"In the interstitial connective tissue there was a moderate amount of edema, which was most marked about the small blood vessels. The capillaries were congested in some places, and occasional foci of extravasated erythrocytes were seen.

"In the lungs, gross and microscopic examination disclosed patchy sites of collapse without evidence of pneumonitis. The capillaries were moderately congested.

"In the central nervous system, the falx, tentorium and leptomeninges were normal. The weight of the brain was 430 Gm. (normal 440 Gm.), and its external appearance was not unusual. On coronal section the reticular substance in the medulla was faintly pink and bulged slightly above the cut surface. A single hemorrhagic

needle tract was seen entering the anterior horn of the left ventricle. The spinal cord was adjudged normal.

"Microscopic examination revealed typical evidence of acute polioencephalomyelitis, with involvement of the cord, medulla, roof nuclei of the cerebellum and the thalami. The sections of the cervical and thoracic parts of the cord demonstrated the severest reaction. In the cervical enlargement the ganglion cells of the anterior columns were destroyed, while a few ganglion cells were still discernible in the posterior columns. These ganglion cells demonstrated marked peripheral clumping of the Nissl substance, with a perinuclear clear zone. Scattered, shrunken, granular, eosinophilic masses were seen in the more reactive zones, which represented ganglion cells that had undergone degeneration by lysis. No neuronophagia or inclusion bodies were demonstrated.

"The inflammatory infiltration was moderately severe. The infiltrate consisted of numerous large mononuclear cells, which frequently displayed a vacuolated cytoplasm. There were also moderate numbers of lymphocytes and plasma cells admixed with a few neutrophils.

"The capillaries were congested and in part surrounded by a cuff of mononuclear cells. The ground substance of the gray matter appeared somewhat soft, but the astrocytes were not unusually prominent.

"In the thoracic segments of the cord the reaction was more pronounced in one anterior column and, in general, not so severe as in the cervical enlargement. Lysis of ganglion cells was apparent, with rare focal accumulations of inflammatory cells. A moderately marked inflammatory reaction was diffusely distributed throughout the anterior and lateral columns. Phagocytic activity by the mononuclear cells was rarely observed.

"In the lumbar segments of the cord there was equal involvement of the two anterior columns in about the same intensity as that of the more severely involved thoracic region.

"In the reticular substance of the medulla there was moderately severe, diffuse destruction of ganglion cells accompanied with light diffuse inflammatory infiltration. The nuclei of the cranial nerves were not conspicuously involved. The roof nuclei of the cerebellum and the thalami contained a few scattered foci of inflammatory cells. Perivascular cuffing by lymphocytes and mononuclear cells was for the most part confined to the sites of parenchymal involvement."

"A review of the literature revealed no previous case in which prodromes in the infant appeared as early as three and one-half days of life. In no reported case had the mother had acute febrile poliomyelitis of four days' duration at the time of birth. In one report the mother had had prodromes the day before delivery, but in that instance the infant did not become ill until the eleventh day of life, after exposure to its mother for 10 minutes on the first day of life. In view of the fairly well established fact that the minimal incubation period of clinical poliomyelitis is five days and that immediate isolation of the infant in the first case was carried out on delivery, his illness appeared either after an incubation of only three and one-half days or resulted from an intrauterine infection. On the basis of this evidence it is no longer possible to assume that newborn infants are immune to poliomyelitis."

The Blood Picture in Exanthem Subitum with Particular Consideration of the First Phase—SAAL, CH.—*Helvetica paediatrica acta*, 5: 291 (June) 1950.

Exanthem subitum may cause considerable diagnostic difficulties, particularly at the onset, and the definite diagnosis is not afforded until the characteristic leukopenia with relative lymphocytosis and neutropenia appears together with the rash and the defervescence.

The author therefore studies the blood picture of the initial phase. About 140 cases of exanthem subitum have been admitted over a period of 17 years, but as in some cases the blood was examined only once and as some children were not admitted until the exanthem had appeared, only 50 cases could be used for this report. The blood was examined in 7 cases on the first, in 24 cases on the second, in 19 cases on the third, and in all cases on the fourth day, at the time of critical defervescence and appearance of the exanthem. The age of the children ranged between 11 days and 2½ years; at this

age the physiologic variations of the blood picture are marked. The total number of leukocytes may normally range between 6,900 and 13,110; the range is 27.5 to 44.3 per cent for the neutrophils, 43.5 to 58.5 per cent for the lymphocytes, 5.0 to 11.7 per cent for the monocytes, 0.5 to 6.0 per cent for the eosinophils, and 0.0 to 1.2 per cent for the basophils. The course of the total number of leukocytes in the 50 cases was little characteristic; the number ranged during the first three days between 2,700 and 16,800, but 26 children showed leukopenic values. On the fourth day definite leukopenia was present in 37 cases, while in the remaining 13 cases the number increased as the minimum had already been reached on the second or third day. A shift to the left was not constant and the staff cells amounted to between 3 and 47 per cent. The total neutrophils, including both staff and segmented cells, were constantly above the norm on the first day; on the second day 20 out of 24 children showed neutrophilic values up to 93 per cent, and on the third day 17 out of 19 children showed values up to 85 per cent. On the fourth day the neutrophilic cells decreased with few exceptions to leukopenic values, even down to 1.5 per cent, suggesting granulocytopenia, but return to normal figures supervened soon. During the first three days of fever the lymphocytes showed a decrease in all but 4 cases, down to 1.5 per cent in 1 case; on the fourth day a relative lymphocytosis of 46 to 93 per cent was present in all cases without exception.

The monocytes have not been considered in the literature to date but the author was able to determine a certain regularity. On the first day 4 out of 7 cases showed an increase above the norm, up to 31 per cent, while the other 3 showed figures within the norm. The majority showed values above the norm on the second day, while most values were grouped around the norm on the third day; on the fourth day the monocytes fell to normal or subnormal values in 41 cases while they rose in 9 cases, in 4 of them above the norm.

The eosinophils disappear almost completely during the first three days and return in small numbers after appearance of the exanthem. No regular behavior could be determined with respect to the plasma cells and basophils due to their small numbers.

Computing average values from all 50 cases, the total number of leukocytes was below the norm on the first day, remained almost constant on the second and third days, and fell rapidly to leukopenic values only on the fourth day. The neutrophils definitely start with elevated figures which they keep during the second and third days, with a decrease to neutropenic values only on the fourth day. The lymphocytes are present in low numbers on the first day, and the lymphopenia persists on the second and third days, with development of the characteristic lymphocytosis on the fourth day. The monocytes start with values above the norm, decrease gradually on the second and third days, and reach values at the lower limit of the norm on the fourth day.

Thus there is slight leukopenia, neutrocytosis, lymphopenia, and monocytosis during the first three days, while the characteristic picture of definite leukopenia, neutropenia, lymphocytosis and normal monocytosis develops only on the fourth day.

Subcutaneous Beryllium Granuloma — Silverman, Seymour B. and Erickson, Cyrus C.—*Archives of Pathology*, 50: 63 (July) 1950.

Recently, an example of subcutaneous beryllium granuloma came under the writers' observation. "The paucity of reported instances, as well as the fact that this lesion bore a striking histologic similarity to Boeck's sarcoid of the Darier-Roussy type, makes this case worthy of note and of particular interest in that it emphasizes the occurrence of this morphologic type of granulomatous reaction as a result of an injury caused by this specific agent, beryllium."

A 12 year old white boy was admitted to hospital complaining of a tender, thick, callus-like palmar scar. "Two years previously he had picked up a cracked fluorescent lighting unit, which fragmented in his hand, causing a 2.5 cm. laceration over the thenar eminence. This failed to heal properly, and the area continued to be tender and annoying.

"Physical examination confirmed the foregoing complaint but gave otherwise

Features Described by Dutra as Significant in the Differentiation Between Boeck's Sarcoid and Beryllium Granuloma

Sarcoid	Beryllium Granuloma
1. Compact mass of epithelioid cells	Typical epithelioid cells rare
2. Giant cells centrally located	Central giant cells rare
3. Giant cells large, with 25-30 peripheral nuclei	Giant cells vary, with 4-30 + nuclei
4. Loose perinodular connective tissue with numbers of lymphocytes	Granulomas infiltrated with moderate numbers of lymphocytes
5. No central necrosis	Most granulomas have fibrinoid material or granular necrotic eosinophilic debris centrally

negative results. The chest was clear. The regional lymph nodes were not enlarged. Laboratory data indicated normal conditions.

"The palmar scar was widely excised, and the patient made an uneventful recovery.

"The surgical specimen, a rectangle of skin and subcutaneous tissue 1.5 by 1.0 by 0.5 cm., was grayish white and rubbery firm. A depressed area of scarring, 3 mm. in diameter, was present in the center of the skin surface. The tissue was fixed in formaldehyde solution U. S. P. diluted 1: 10, sectioned at 6 microns, and stained with hematoxylin and eosin, Masson's trichrome stain, Foot's reticulum stain, the Verhoeff-van Gieson elastic tissue stain and acid-fast stains for tubercle bacilli.

"Histologically, the epidermis revealed hyperkeratosis, acanthosis, some elongation of the rete pegs and slight spongiosis, mainly in the stratum spinosum. The cutis was composed of dense parallel bundles of collagenous fibers, and in the papillary and reticular layers there were focal perivascular collections of lymphocytes and macrophages. In the remainder of the cutis, especially in the lower half, and extending down into the subcutaneous fat, there were numerous discrete and confluent tuberculoid granulomatous nodules embedded in a dense connective tissue stroma. The granulomatous process consisted of typical epithelioid cells, lymphocytes, macrophages and large, multinucleated giant cells of both Langhans' and foreign body types. Many of the granulomas were well encapsulated by concentrically arranged bundles of collagenous fibers, and related to many of them were collections of lymphocytes. Connective tissue replacement was conspicuous, and all degrees, from early fibroblastic cell proliferation to almost complete fibrosis, were seen. A very few of the lesions showed small central foci of granular debris, but this was absent in most instances. No foreign body material was present, nor were any inclusion bodies noted in the giant cells. No doubly refractile matter was demonstrated. The acid-fast stains were negative. The Verhoeff-van Gieson stain revealed loss of elastic fibers in the superficial areas of scarring, but they were seen about some of the granulomatous nodules. Foot's reticulum stain showed this substance to be present within some, but not all, of the nodules."

There is a marked similarity in histologic appearance of beryllium granuloma and the Darier-Roussy type of Boeck's sarcoid. "In the absence of an adequate history it is doubtful whether the two can be differentiated on histologic grounds alone. In a study of beryllium pneumonitis, Dutra considered certain features by means of which, in his opinion, differentiation was possible. These included the position of the giant cells, the number of nuclei in the giant cells, the presence or the absence of central necrosis and the relative numbers of epithelioid cells (see table).

"An attempt to apply these criteria to the case herein presented emphasized not only the difficulty of assigning any diagnostic specificity to the histologic picture of this lesion but, even more, the morphologic similarity of the granulomatous reactions produced by apparently unrelated agents of disease. For instance, epithelioid cells were by no means rare; the giant cells were situated as often centrally as peripherally; the number of nuclei in the giant cells varied from 8 to 46, but half of such cells possessed 25 to 30 nuclei;

fibrinoid or granular necrotic debris was rarely seen in the center of the granulomas.

"From a consideration of the foregoing facts it appears that although certain minor differences in the appearance of the lesions of Boeck's sarcoid of the Darier-Roussy type and beryllium granuloma may be present, yet the over-all pictures are so similar that differentiation on morphologic grounds alone seems highly unlikely."

Chloromycetin Treatment of Typhoid and Paratyphoid Fever in Childhood — HATZ, F.—*Annales paediatrici*, 175: 121 (July-August) 1950.

After a survey of the literature the author reports his own observations. His first case concerned a boy, aged 28 months, who had a tonsillitis with fever of a few days' duration and two weeks later suddenly developed abdominal pain, high fever, and first constipation and later diarrhea, without blood in the feces. After a week a physician was consulted and paratyphoid B bacilli were found in the stools on three occasions. Ten days after onset an abdominal roseola appeared. Defervescence was slow. Three weeks after onset suddenly swelling and pain appeared at the level of the left elbow and the temperature rose again. Examination on admission six days later showed doughy swelling over the elbow tip and along the proximal ulnar margin, moderate effusion in the elbow joint, pain on movements, avoidance of active movements while passively complete extension and flexion were possible, tenderness of the bones in the area of the doughy swelling, no swelling of the regional lymph glands, and a negative roentgenogram of the left elbow. Physical examination was otherwise negative. The sedimentation rate was 63 mm. and 72 mm. after one and two hours respectively. The urine contained traces of albumin. Stool cultures were negative for paratyphoid B bacilli.

Antiphlogistine packs were applied locally. After 10 days the temperature rose to 39° C., and then remittent fever persisted. Another roentgenogram was negative and stool cultures were also negative. The elbow joint was immobilized on a plaster splint and chloromycetin treatment was instituted; 250 mg. were given every four hours to a total of 10.25 Gm. General condition, fever, and local symptoms were not influenced by this treatment. Streptomycin treatment was then instituted with a dosage of three injections of 200 mg. each daily but also proved ineffective. After three weeks the roentgenogram showed a definite periosteal reaction at the level of the upper ulnar margin, and surgical excochleation was then carried out, with drainage with gauze soaked in streptomycin. Macroscopically the bone appeared normal but microscopically mild osteomyelitis was demonstrable; cultures of the bone fragments were negative. Postoperatively the pain improved, mobility of the arm also improved, the periosteal defect became calcified, and the temperature became normal within four weeks. On discharge pronation and supination were still slightly limited, and some nontender swelling of the elbow persisted. The general condition was good.

The second case concerned a boy, aged 12, who was taken ill with headache and high fever; vomiting supervened, meningism was diagnosed and penicillin treatment was instituted. After five days the boy was sent to the hospital with a diagnosis of tuberculous meningitis. Examination showed a tense slightly distended nontender abdomen; the lower pole of the spleen was palpable at the costal margin while the liver was not enlarged. The spinal fluid was normal and chest fluoroscopy showed normal results. Blood and stool cultures were negative. After three days the agglutination for paratyphoid B became positive 1:200. On the eleventh day of the disease the temperature became remittent and chloromycetin treatment was instituted; after an initial dose of 1.5 Gm. (50 mg. per Kg. body weight) 250 mg. was given at intervals of three hours until defervescence and then decreasing doses were given for another three days. The total dosage was 9.25 Gm. Defervescence supervened 48 hours after institution of treatment and at the same time the general condition definitely improved. Nineteen days after admission the temperature rose again slightly and pain appeared at the level of the left arm where the muscles became tender. The roentgenogram was negative. The slight temperature elevation persisted for three days, with hardly any impairment of the general condition. Para-

typhoid neuromyositis was assumed. Subsequently the left wrist became tender and was still slightly tender on discharge after seven weeks.

The third case concerned a girl, aged 3, who was admitted on the eighth day of a typhoid fever infection, with positive blood and stool cultures and a positive agglutination. On the tenth day chloromycetin treatment was instituted; after an initial dose of 375 mg. (25 mg. per Kg. body weight) 250 mg. was given at intervals of four hours until defervescence which supervened after 108 hours, and subsequently 250 mg. was given at intervals of eight hours for another week. The general condition improved three days after institution of the treatment. There were no complications. At the end of the fourth week three stool cultures were negative and the girl was discharged cured.

The fourth case concerned a boy, aged 4, who developed paratyphoid B after ingestion of large amounts of raw milk. The boy was admitted on the eighth day of continuous fever. On the tenth day the blood culture was positive; the stool culture was negative and the agglutination was positive. Chloromycetin was started with an initial dose of 25 mg. per Kg. body weight, followed by 250 mg. every four hours until defervescence which supervened after four days, and subsequently 25 mg. was given every eight hours for five more days. During the fifth week three stool cultures were negative and the boy was discharged cured.

The fifth case concerned a girl, aged 21 months, with paratyphoid B; the fever was continuous until the tenth day and the agglutination was positive on the fourteenth day. On the tenth day chloromycetin treatment was instituted; for five and a half days 250 mg. was given every six hours, and then for eight days the same dose was given every eight hours. Defervescence and improvement of the general condition supervened after three days of treatment. During the fifth week three stool cultures were negative and the girl was discharged. In this case the period of remittent fever could be completely suppressed by the chloromycetin treatment.

The sixth case concerned a girl, aged 33 months, with paratyphoid B; the fever was continuous until the ninth day and then remittent. On the ninth day the agglutination was positive and on the twelfth day the stool culture was positive. On the eleventh day chloromycetin treatment was instituted; for three and a half days 250 mg. was given at intervals of six hours and subsequently the same dose was given every eight hours for eight days. The child became afebrile within 24 hours and the general condition improved. During the fourth week three stool cultures were negative.

From these few cases no definite conclusions concerning the efficacy of chloromycetin treatment can be drawn. In the case of typhoid fever the period of remittent fever was definitely shortened and recovery was hastened; the same applied to the 4 cases of paratyphoid B, and the complicating neuromyositis in 1 of them could be attributed to a too short chloromycetin aftertreatment. In the first case of paratyphoid fever the primary affection could not be treated and the development of the periarthritic focus was not influenced by the chloromycetin treatment.

No definite dosage plan is as yet available. The drug was well tolerated and no side effects were observed. Continuation of treatment with a dosage reduced to one half for eight days after defervescence seems advisable.

Progress in the Treatment of Childhood Croup — Windorfer, A. — *Deutsche medizinische Wochenschrift*, 75: 923 (July 14) 1950.

Croup is a febrile syndrome in which hoarseness and even aphonia, and a typical cough develop, followed by dyspnea which may reach the stage of suffocation; loss of consciousness will result from excessive carbon dioxide of the blood and at this stage the circulatory damage may have become so intense that even freeing of the respiratory passage will not save the life. It involves chiefly young children and its peak concerns the second to third year of life.

Usually four stages of croup are distinguished; namely, hoarseness, stenosis with dyspnea, cyanosis and asphyxia but the transitions are not sharp and clinical distinction of the stages is not always possible. While the croup of diphtheria

has markedly decreased in frequency, inflammatory laryngeal stenoses can be provoked by other infections, like the grip croup which represents a nonspecific laryngitis caused by streptococci, staphylococci and pneumococci; the severe form of this affection, with edema and even pseudomembrane formation, has been termed acute infectious laryngotracheobronchitis. Furthermore measles croup may be observed either during the prodromal stage or after disappearance of the rash, caused in about half the cases by diphtheria. Scarlet fever croup and whooping cough croup are more rare and are also usually caused by infection of the larynx with cocci. Pseudocroup is excluded as it represents a predominantly allergic reaction, lasts only a few hours, is not associated with fever, or with alterations of the voice, and may be considered as "asthmatic attack of the larynx."

Tracheotomy was not very successful in the treatment of croup and carried a mortality of 60 to 80 per cent while the mortality was reduced to 36 per cent after introduction of treatment with diphtheria antitoxin. Intubation is preferred to tracheotomy by large clinics but the mortality is still high. Improvement has been achieved since the introduction of direct laryngoscopy and aspiration of the membranes. All mechanical methods are limited by the impossibility to reach the obstructing lesions of the lower portions of the respiratory tract and a true etiologic treatment of nonspecific croup and improvement of serum effect in the croup of diphtheria are desirable.

Over a period of 13 years the author observed 638 cases of croup, with 105 deaths; the mortality rate was 29 per cent for croup of diphtheria and 4.6 per cent for grippal and other types of croup. The deaths amounted to 36 among 89 intubations, to 33 among 65 cases of intubation and secondary tracheotomy, and to 6 among 14 primary tracheotomies; thus only 55.5 per cent of all children requiring an intervention could be saved. In cases in which no intervention was carried out, 30 deaths occurred. Apart from suffocation bronchopneumonia is the most frequent cause of death in croup, and the pneumonia after intubation or tracheotomy could not be prevented or controlled as satisfactorily as other pneumonias with sulfonamides or penicillin. The cause of the poor response to treatment is to be found in the special pathogenesis of this form of pneumonia; the most important factors are poor aeration, with subsequent insufficient blood supply of the lungs and stasis, aspiration with the tube in place, defective cough due to lack of expulsive force and drying of the secretions.

Observation of an excellent result with penicillin treatment in a case of severe croup in which an intervention had at first seemed unavoidable led the author to institute penicillin treatment in all but a few very mild cases of croup. A total of 68 cases of croup was observed; 53 cases of variable severity were treated with penicillin, 13 mild cases were treated without penicillin, and 2 children, admitted in the acute attack of suffocation, required intubation and secondary tracheotomy. There were no deaths in this series. Of the 53 cases treated with penicillin 13 seemed so severe that according to experience an intervention would have become necessary. In addition to the lifesaving effects penicillin treatment shortened the duration of the disease in diphtheria from 29 to 16 days and in grippal croup from 13 to 9 days. The incidence of complications was also decreased. No complications were observed in 15 cases of diphtheria, and the incidence of bronchopneumonia in grip was reduced from 18 to 5 per cent.

The efficacy of penicillin treatment in nonspecific laryngitis is easily explained as usually streptococci, staphylococci or pneumococci are dealt with, and the same applies to sulfonamide treatment as recommended earlier. In diphtheria the results are better with penicillin and serum than with the latter alone; the penicillin prevents, by its specific antibiotic effect, progress of the specific process and at the same time cures the usually concomitant nonspecific laryngitis. Diphtheria bacilli are about one-hundredth as sensitive to penicillin as streptococci; their sensitivity varies with the strain.

The bacilli of recently affected individuals are more sensitive than those of carriers. The only slight efficacy of penicillin in pharyngeal diphtheria is not to be used as an argument against its efficacy in

laryngeal diphtheria, as in the former the toxic effects are the dangerous ones, while in the latter the mechanical stenosis represents the main danger.

As at the onset of the affection, a definite differential diagnosis between diphtheria and grippal croup is usually impossible, serum is given routinely in a dosage of 8,000 to 10,000 units for infants and 10,000 to 20,000 units for older children. Fermo serum should be used as otherwise serum disease may lead to aggravation of the laryngeal edema. In severe cases, penicillin treatment is started immediately with a dosage of 50,000 units intravenously every three hours. A penicillin spray may be helpful but must not disturb the patient's rest. The penicillin injections may increase the cough but this should not lead one to discontinue treatment. The usual supportive measures, including sedative and alcohol, should not be neglected. Accurate medical supervision and good nursing care are of the greatest importance; acute attacks of suffocation may still require an intervention. The aim of penicillin treatment is early control of the infection and prevention of dyspnea and interventions; as it cannot be decided in the beginning which cases will become severe, penicillin treatment should be instituted routinely.

Tularemia as a Pediatric Problem — Levy, Harold B., Webb, Clarence H. and Wilkinson, Jacques, D. — *Pediatrics*, 6: 113 (July) 1950.

"Forty-eight cases of tularemia in childhood were observed over a six year period."

It has been customary to classify tularemia into four types according to the clinical picture: ulceroglandular, typhoidal, glandular, and oculoglandular. "The comparatively large number of instances in which primary involvement occurred in the pharyngeal and tonsillar area requires the inclusion of a fifth and rather important type, which has been designated as 'pharyngo-tonsillar.' While the ulceroglandular form predominated with 21 cases, it constituted only 44 per cent of the total, with the pharyngo-tonsillar group totaling 11 cases. . . . Typhoidal tularemia was seen in 8 instances, glandular in 6 and oculoglandular in 2, one of which was combined with pharyngo-tonsillar involvement."

"In 15 patients, the tularemic infection was introduced through the ingestion of insufficiently cooked infected material, usually rabbit or squirrel. Tick bite was almost equally important, occurring 14 times. Direct animal contact accounted for only 11 infections, while the actual source was uncertain in 7. One child had both contact (oculoglandular) and ingestional (pharyngo-tonsillar) tularemia."

"It may be of diagnostic significance to reclassify clinical groupings as they appear in the infant (0 to 2 years), preschool child (3 to 6 years) and school child (7 to 12 years). In the series reported here, the lone infection occurring under 2 years of age was typhoidal tularemia, while in the preschool group there were 5 instances each of pharyngo-tonsillar and typhoidal forms, with only 4 of ulceroglandular and 3 in other classifications. In the older children there were 17 patients with typical ulceroglandular tularemia, only 6 with pharyngo-tonsillar, 2 typhoidal and 5 falling into other categories. Hence the older school child presents a picture more closely resembling that seen in adults; the younger child is more apt to have pharyngo-tonsillar and typhoidal forms.

"Sources of infection follow a somewhat similar age pattern, with the single case in infancy attributable to ingestion, and the preschool children showing 7 infections from ingestion, 6 from tick bite and 4 from other sources. In the older age group, the adult configuration was more closely approached, with 11 cases from direct animal contact, 8 from tick bite, 7 from ingestion and 4 from other sources."

"Ulceroglandular. — Ulceroglandular tularemia in this series differs little from the classical description of the disease as it appears in the adult, except for the fact that more than half the infections developed following tick bite, while only 9 followed contact with rabbits and 1 with an infected squirrel. The combined animal sources, with 1 instance of tick bite on the elbow, made the extremities the most common location for the primary lesion; however, there were 6 cases, all due to tick bites, in which the initial site appeared on the genitalia. Other sites included the thoracic wall, neck and iliac

crest. The complex of primary lesion with regional lymphadenopathy suggested the admitting diagnosis of ulceroglandular tularemia in 15 of the 21 cases of this type. Pyogenic infection was considered in 4, while other conditions suggested included brucellosis, tuberculosis, typhus, acute disseminated lupus erythematosus and rheumatic fever. Further complicating the diagnostic picture was the presence of tularemic septicemia with pneumonic involvement in 6 patients. Fortunately, the first child survived with supportive care and specific therapy was available for the last 5, so that no fatalities occurred in the ulceroglandular group.

"Pharyngo-Tonsillar.—The importance of ingestion as a source of tularemic infection becomes apparent in reviewing the pharyngo-tonsillar group, since 9 of the 11 in this category gave a history of having eaten infected material. One case followed a tick bite on the neck and in the other the source was uncertain. Diagnosis was considerably more complex in this group, due to their resemblance to follicular tonsillitis, which was suspected in 8 instances. Vincent's angina and typhoid fever were each considered 3 times, while the suggestion of diphtheria was sufficiently strong to justify administration of antitoxin in 2. Tularemia was not considered in initial differential diagnosis and evaluation was made only after careful questioning and clinical study. The description of a shaggy, necrotic exudate involving the pharyngo-tonsillar area, with marked cervical adenopathy, has been described. . . . The majority of children in the present series who had pharyngo-tonsillar tularemia came from families wherein other members were infected. The first 3 patients seen were admitted with the father, who later died of the disease. In the next case, the father had died of tularemia just prior to the child's admission to the hospital. Two others were siblings, admitted together and subsequently diagnosed as having pharyngo-tonsillar tularemia. Septicemic involvement occurred in 5 of the 11 cases, with 1 death, giving a mortality rate of 9 per cent in the pharyngo-tonsillar group.

"Typhoidal.—Ingestion as a source of tularemia is again significant in the typhoidal form, as 5 of the 8 cases acquired their disease in this manner. Two became infected from tick bites; in the remaining case the origin was obscure. Initial diagnostic considerations ranged from meningitis in 3 instances to brucellosis, rickettsial infection and even poisoning. Tularemia was thought of in the last 2 patients, as they were siblings admitted together. There were 3 other instances of sibling involvement in this group. Three of the 8 children with typhoidal tularemia died (2 within a few hours after admission).

"Glandular.—Cryptogenic infection was seen in 6 patients, only 1 of whom had a definite history of ingestion, the sources of infection for others being uncertain. Cervical adenopathy was outstanding in 5 patients; the sixth had pronounced axillary adenopathy. Tuberculosis was considered in 4 instances, pyogenic infection in 3 and Hodgkin's disease once. Only twice was tularemia thought to be likely on admission to the hospital. There were no fatalities in the glandular group.

"Oculoglandular.—This interesting form was observed in 2 cases, both following contact with diseased rabbits. Trauma to the eye was reported in the history of 1, while the other resembled tuberculosis. This latter case also showed tonsillar involvement, giving a history of eating and handling presumably infected material. Both children recovered, even though the present therapeutic agents were not available."

The agglutination reaction, confirmed the diagnosis of tularemia in all instances, with exception of 3 fatal cases and 1 other. "However, this important test does not become useful until the eighth to tenth day of the disease, hence is of little diagnostic value in equivocal cases just when specific therapy is most urgent." To overcome this defect, an intradermal skin test has been developed which is reputedly positive in 92 per cent of cases in the first week of disease. "The requisite of species-specific serum and the unreliability of the commercially produced serums limit use of the skin test by the average practitioner. The skin test was not used in the present series. Blood cultures may be of assistance early, but technical difficulties and extreme dangers to laboratory workers preclude widespread use of this means.

"The appearance of numerous cross agglutination phenomena added to the diagnostic difficulty. These included not only *Brucella abortus* and Proteus ox 19 as usually described, but also the heterophile antibodies. A recent study has shown that a number of conditions other than infectious mononucleosis may produce positive heterophile reactions, but to date the authors have found no mention of cross agglutination with tularemia. A positive heterophile reaction was obtained uniformly in the 24 cases tested in the present series, the majority showing titers in excess of 1:112 or 1:224. The reaction was obtained as early as the sixth day of the disease, and showed gradual rise in many instances, in contrast with other cross agglutination reactions which declined and then disappeared."

Therapy with many agents in the preantibiotic era met with little success until a specific antiserum was developed. Following a demonstration of streptomycin effectiveness in experimental tularemia, evidence rapidly accumulated concerning its therapeutic value in human infection. "A recent comparative study indicates its superiority to immune and hyperimmune serums. . . . Atabrine and aureomycin have been used, the latter apparently with considerable success although studies are still in the experimental stage."

Twenty-four patients received streptomycin therapy. "Due to the limited supply and uncertainty as to dosage at the onset, there has been some irregularity in dosage schedules. The average total dosage used was 8.37 Gm., given over an average period of 7.46 days. One child with pharyngo-tonsillar tularemia and septicemia received as much as 15.2 Gm. within a nine day period; another with uncomplicated ulceroglandular infection required but 1 Gm. daily for only four days." Even this amount may be in excess of actual requirements, since one author recently indicates the optimal dosage as 0.5 Gm. daily for two days, followed by 0.25 Gm. daily for four days; or 0.5 Gm. daily for six days.

"Response was usually prompt and complete, with drop in temperature and amelioration of symptoms within 48 hours in practically every instance."

"There were 4 deaths among these 48 patients, but 3 of these occurred in the 8 who had the dangerous typhoidal type of tularemia. The other death occurred in a patient who had pharyngo-tonsillar tularemia. Two of the patients died within six hours after admission."

The Interstitial Pneumonia of Prematures—FREUDENBERG, E. AND TOBLER, W.—*Annales paediatrici*, 175: 185 (July-August) 1950.

The authors use the term of interstitial pneumonia, based on anatomic findings, rather than that of plasmacellular pneumonia against which serious objections have been advanced; undoubtedly this affection occurs in mature infants as well as in prematures but the latter are predominantly involved. A questionnaire was sent to all pediatricians and pathologists of Switzerland and a total of 707 cases of interstitial pneumonia of the premature was found over a nine year period, with 154 deaths. This affection is definitely a disease of institutions; among the authors' 380 cases there was none which had followed a home delivery and exclusive home care, and the scanty cases sent to the hospital from the outside came from infant homes or obstetric institutions or had spent some time in such institutions. The age range involved is that between 6 and 16 weeks, with a peak between the ninth and thirteenth week. The largest number of deaths concerned the group with a birth weight of 1,500 to 2,000 Gm. in Bern, and that with a birth weight between 2,000 and 2,500 Gm. in Basel; the mortality rate was 15.9 per cent in Bern and 18.1 per cent in Basel. Statistics definitely demonstrate that infants with a lower birth weight develop the affection more frequently than those with a higher birth weight within the premature group; the more immature an infant the greater is the danger of developing the affection if exposure is present. In institutions with favorable hygienic conditions, mature infants are hardly endangered even when exposed during the most dangerous period of life.

For explanation of the special danger to prematures some authors refer to immaturity of the lung tissue as predisposing factor while others refer to disappearance

of the antibodies transmitted from the mother; the latter conception is supported by the interval of several weeks' length between birth and onset of the disease. For the past six years the authors have considered this affection as an infectious disease and a special predisposition must be assumed against a pathogenic agent which is not pathogenic for normal adults and older infants and only very weakly pathogenic for mature young infants.

The highest number of cases was observed during the second fourth of the year, but a definite seasonal predominance cannot be concluded from the statistics. The female sex showed a 15 per cent higher involvement but as the sex distribution among the exposed infants was not determined this difference cannot be considered as essential.

The clinical picture is characterized by the discrepancy between severe dyspnea and slight or even lacking physical findings; the authors stress the importance of the respiratory rate in infants, and any increase above 40 to 50 in prematures is suspicious of interstitial pneumonia although it does not establish the diagnosis. Roentgenologically the frequency of emphysematous conditions which produce irregular, often vesicular clearings in the diffuse shadow is important, and anterior marginal emphysema is particularly frequent; mediastinal and even cutaneous emphysema has been observed by the authors. Fever is lacking in the vast majority of cases, very often the weight curve is unimpaired, and even the stools are only exceptionally altered. The sedimentation rate is usually only moderately elevated or not elevated at all, but in some cases it shows a marked increase. The authors' observations do not definitely demonstrate that a marked rise of the sedimentation rate indicates mixed infection. A definite shift to the left of the white blood picture and marked leukocytosis are observed only occasionally; the authors found a shift to the left in only 17 out of 145 hematologically studied cases. The eosinophils amounted to more than 5 per cent in 40 per cent of the cases. The monocytic blood elements predominated over the granulocytic ones in the vast majority of cases, perhaps partially due to the age group dealt with. Bone marrow punctures done in 4 cases during life, and bone marrow smears on autopsy showed no impairment of the hematopoiesis; 1 case showed definite eosinophilia of the bone marrow. The absence of juvenile and immature lymphocytes and the negative or insignificantly positive cold agglutinin test distinguish interstitial pneumonia from the atypical or virus pneumonia of American authors. The authors believe that interstitial pneumonia is a virus pneumonia, but with a virus different from that of atypical pneumonia, particularly as older children usually do not develop the disease on exposure.

Some prematures were discharged in good condition and had to be readmitted after some time with definite signs of interstitial pneumonia; this happened less frequently in Bern where all prematures are kept in the hospital until the age of 3½ months because of the possibility of interstitial pneumonia, than in Basel where they are often discharged earlier; the mortality in these cases was definitely higher, probably because at home the diagnosis was not made early enough and an advanced stage was reached at the time of readmission.

As it may be assumed that infection with interstitial pneumonia always takes place in the institution and never at home the intervals between hospital admissions give a clue with respect to the incubation period. In Bern 4 cases with intervals of 30 to 42 days were observed, and in Basel 10 cases with intervals of 30 to 40 days, 6 with intervals of 42 to 49 days, and 1 with an interval of 59 days. A few days may have to be deducted as the diagnosis is not immediately made at home, but it is unlikely on the other hand that the infection took place on the day of discharge from the hospital. Therefore incubation periods of 30 to 50 days must be admitted. This would indicate that prematures are infected very soon after admission to the institution as the incubation period corresponds to the beginning of the curve of age distribution of the affection.

Contagiosity of interstitial pneumonia is indicated by the following observations: 1. The cases observed in an institution form groups, often with prolonged intervals between them, and sometimes veritable chains of infection are observed. 2. The

affection is frequent in institutions for infants while infants at home are spared. 3. There are variations in the course of years and seasons. 4. Strict isolation and terminal disinfection have a definitely favorable effect.

Bacteria can be excluded as causal agents. Pneumococci are not found on lung puncture, cultures are negative, and penicillin is completely ineffective. The age cannot be made responsible for the peculiar form of the pulmonary affection as prematures of the same age may occasionally develop typical bronchopneumonia with a completely different clinical and anatomic picture. A virus etiology is admitted by the authors; there is no relation to the common catarrhal infections of the respiratory tract and colds and coryza.

The authors tried prophylaxis with injections of human gamma globulin during the fifth, seventh, ninth, and later also eleventh week of life on the basis of the conception of disappearance of the antibodies transmitted from the mother; the material is too small to evaluate the value of such prophylaxis. An attempt of prophylaxis with pantothenic acid was ineffective.

Therapeutically good nursing care, early and abundant administration of oxygen with 5 per cent carbon dioxide, and analeptics are the most important measures; because of mixed infections sulfonamide treatment is advisable but has no effect on the basic affection. Short-wave diathermy, roentgenotherapy, chloromycetin and aureomycin have been used but the results cannot as yet be evaluated.

Symposium Section

Syringe-Borne Infections

The transmission of diseases by contaminated hypodermic syringes has been known about as long as they have been used even though the routine of boiling both the needle and syringe has been followed by all with the possible exception of drug addicts. Any danger of infecting an individual has been considered improbable if sterilization is practiced. But for the last two decades experiences have occurred in the practice of the most careful which definitely indicate that ordinary precautions are not as safe as formerly thought. This is doubtless due to the enormous increase in the number of drugs and other materials given by injection as well as to venipuncture incidental to blood collection for so many tests or so much blood chemistry. Blood collection at banks and the use of the parenteral route for so many combinations which have been found most helpful to our therapy, have also contributed to the hazard which we have called syringe-borne infections.

Luckily most of the more serious accidents, such as infections with syphilis, malaria, many pyogenic infections and even tuberculosis, which are recorded can be traced to gross failures in technic, but others have been attributable to methods of sterilization in common use. These were entirely adequate in the past but the transmission of many conditions not previously known has shown that these methods must now be changed.

Among the earlier accidental infections malaria and syphilis were the most frequent to interest medical writers, and they were for the most part transmitted by transfusions from donors who were not checked sufficiently to rule out these conditions. However, there were other ways which were more common than is generally known. These were among addicts who had reached a level where they had become totally irresponsible. One example of this type of syringe-borne infection which came within our own experience occurred in old Charity Hospital in New Orleans during the latter half of 1932 and most of 1933. During that period, and it seems long before, the existence of malaria had been proved by blood smears in almost all of the drug addicts which were seen in outpatient clinics or admitted to hospitals or prisons. Investigations to determine the cause resulted in revelations which were most interesting. Coincidently, similar investigations were being conducted at Cook County Hospital in Chicago, and as the results were strikingly parallel we will report those of Eaton and Feinberg[1] of Cook County to illustrate. It seems that it is a custom among drug addicts to congregate in groups of three or more for pooling their resources and receiving their individual share of dope from the one delegated to obtain it. We have since learned this custom is widely prevalent. In any event the drug (usually morphine) is dissolved in tap water and, because they cannot afford a hypodermic syringe, they draw the solution up into a medicine dropper. Strips of paper are wrapped around the tip so that the hypodermic needle, which they are able to buy, can be attached without leaking very much. The first addict inserts the needle in the vein and as usual a small amount of blood flows back into the dropper. He then injects the amount allotted to him and passes the improvised hypodermic outfit on to the next individual, who takes his share together with whatever blood may be mixed in the solution. This may be repeated from one to another, and the manner in which the plasmodia are transmitted to those previously free of infection is not difficult to imagine.

In the vernacular of "skid row," this method of administering the drug was spoken of as "getting a shot in the main line."[2] The possibility of getting many

1. Eaton, L. McKendree and Feinberg, S. M.: Accidental Hypodermic Transmission of Malaria in Drug Addicts, *Am. J. M. Sc.*, **186**: 679 (November) 1933.
2. Editorial: Transmission of Malaria in Drug Addicts, *Internat. M. Digest*, **23**: 380 (December) 1933.

other things, of which malaria might be the least, was recognized even in those days. Of more than ordinary interest, therefore, was the more recent report by Luttgens[3] of the acquisition of endocarditis by opium addicts who received the drug in the "main line" by the exact same method which was described in 1933. Luttgens encountered 11 cases in a three year period from 1944 to 1946. He carefully studied these cases and found that nonhemolytic streptococci were the infecting organisms in the majority of cases and that the clinical picture and course of infection with these organisms were much the same. Naturally diagnosis in some of these cases was not simple but Luttgens proved his impressions in all of them. The clinical signs were conventional in most cases. The aortic valve was involved in 9 of the 11 cases and the ease with which the murmur of aortic insufficiency was heard aided greatly in the diagnosis. The aortic lesion was predominant in cases in which the mitral valve was also involved although involvement of the mitral valves appeared to be secondary in most of the cases. Preexisting heart disease, rheumatic history and syphilitic heart disease did not appear to be predisposing factors although 9 of the patients were syphilitic. There seemed to be every evidence that the valves finally succumbed to attack after repeated injections of bacteria into the "main line" with these primitive and filthy syringes.

Although Bernheim, in 1917, had demonstrated the transmission of syphilis by transfusion[4] of the blood of infected donors, wide interest was not apparent until the late twenties and early thirties when the practice of blood transfusion was becoming more frequent and the occurrence of both malaria and syphilis was noted especially in drug addicts. Excepting to note the transmission of syphilis by syringe injections, there is probably no point in including here the conventional technic of transfusion as a "syringe-borne infection." But the use of blood fractions, especially convalescent serum, was likewise becoming more frequent during the same period. About this time much concern was being aroused by infections following venipuncture as well as curiosity as to the cause. Prior to the complete iron curtain "black out," which was not yet thought of in the early thirties, scientific information was coming out of the Soviet Union.

Included in this information was an astonishing announcement concerning the use of the blood of cadavers to prevent others from becoming this kind of donor. It seems that a Dr. Judine,[5] head of a hospital in Moscow, conceived this idea due to the implication that "the problem in Moscow of getting donors for blood transfusion was long a puzzle because of the number of patients in need of transfusion." We recall that at the time this assertion stunned us but this was before we learned their routine "double talk." Judine was inspired by earlier experiments performed by a Dr. Chaumow, in 1928, on dogs. The first case in which Judine used cadaver blood, which some later called "canned blood," was that of a man who attempted suicide by cutting the veins of the forearm with a razor. The patient was said to be moribund, so Judine took the blood from a man, aged 60, who had been dead six hours from fracture of the skull. He opened the abdomen of the deceased and from the vena cava withdrew 450 cc. of blood which he injected immediately into the veins of the patient. A few minutes later, it is said, the pulse rate increased and four days later the patient left the hospital. This was another pioneer discovery for the Soviets which they recorded with the others they have claimed. Judine did say he does a Wassermann on all such blood, so the benefit of doubt as to typing and other prerequisites is granted. Moreover, the credit of this discovery will be conceded to the Soviets because a more grim or gruesome source of blood for transfusion could hardly be conceived anywhere else. We wonder what Ivan Petrovich Pavlov and Vasilii Vasilovich Stroganoff would think of this ghastly practice. There is no possibility that syringes will transmit any infections of this sort outside of the iron curtain but it seemed desirable to include it "for the record."

The danger of syringe-borne infection is, of course, inexcusable but it is the in-

3. Luttgens, William F.: Endocarditis in "Main Line" Opium Addicts. Report on 11 Cases, *Arch. Int. Med.*, **83**:653 (June) 1949.
4. Editorial: Transfusions and Syphilis, *Internat. M. Digest*, **22**: 189 (March) 1933.
5. Editorial: Canned Blood Again, *ibid.*, **29**:384 (December) 1936.

fections which hitherto had not been expected and which have occurred in spite of the conventional precautions that are now attracting wide attention. With increased use of syringe-injected antibiotics and the materials used in mass immunizations the danger of syringe-borne infections has become a real hazard.

The transmission of hepatitis by means of contaminated syringes has been recognized and described only within the past 10 years. So it seems appropriate briefly to outline the early observations on this form of jaundice. One of the first discoveries was that it seemed definitely related to the increased use of blood and its products. After eliminating the usual causes, evidence seemed to indicate that a certain number of apparently normal individuals were carriers of an icterogenic substance in their blood which could contaminate a pool of blood or any of its derivatives which were otherwise free of it. This substance became known as the hepatitis-producing agent and the clinical condition caused by it is now known as homologous serum hepatitis. It is said to have been noticed first in England following the use of measles convalescent serum, but it attracted wider attention when it occurred in so many who had received yellow fever vaccine which was widely used in the early part of the war. Little attention was attracted at first because the jaundice usually did not appear until 60 to 150 days after yellow fever vaccine containing human serum had been used. In the interim the many individuals injected had moved far away where it was quite reasonable to assume that other commoner causes of hepatitis might have contributed to the jaundice.

Interest became more widespread in 1942 when two large outbreaks of jaundice followed the inoculation of a group of Brazilians with certain batches of yellow fever vaccine containing human serum. These were followed by epidemics in England among individuals who had received mumps convalescent serum from apparently healthy donors, recipients of yellow fever vaccine containing pooled serum from transfusion centers, and in surgical patients infused with pooled, presumably normal, human serum. All of these incidents had been related to pooled products, but in 1943 Beeson reported 4 cases resulting from transfusions of whole blood. Similar episodes occurred in all parts of the world during the years which have followed.

Elsewhere in this issue* we have abstracted two of the most recent articles which have been published and there seems to be no point in covering this subject any further.

Conclusions reached by Sherwood summarize the condition at the present time. "A 44 per cent incidence of syringe-transmitted hepatitis with jaundice occurred in a group of hospitalized diabetic patients. The icterogenic agent apparently was transmitted by the multiple-dose-per-syringe technic of administering insulin. The incubation period ranged from a minimum of 64 days to a maximum of 106 days, and is compatible with that seen in homologous serum jaundice. The precaution of employing a fresh, sterile syringe and needle for any injection or blood collection will greatly reduce the hazard of disseminating infected serum from patient to patient."

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* See pages 199 and 203.

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The Aging Heart

T. S. Eliot in his poem "Geronition" gives an impressive description of senility. It is a picture of utter defeat. It is a disease that begins with amiable acceptance of the idea that the old have had their day so that when retirement comes the busy man is glad to leave his business to spend the rest of his life in ease and amusement. With no imperative duties and nothing much to look forward to, he potters about and lives in the past; from disuse his faculties soon begin to atrophy and this attitude becomes fixed into an irreversible change. Fortunately, this is not as yet a common disease, but under the increasing stress of overpopulation and Marxian principles it may become so. That it is largely avoidable is the justification for geriatrics. This attitude to old age is based on a false assumption; that the battle is for the strong is only true of the jungle. If we believe that life is the expression of a purpose, fulfilled in many ways, in which the young, the middle-aged and the old all have their part to play, the final touches being essential for its completion, no one of whatever age need be obsessed by a sense of his own futility. While it is desirable that aging people should respect their limitations and be aware of the hazards of old age, the aim of geriatricians should be to impress them with their abilities rather than to emphasize their disabilities. As abilities depend very largely upon the condition of the cardiovascular system, the problem of the aging heart is of crucial importance.

Penicillin in Osteomyelitis

The results of treatment with penicillin in 67 cases of acute hematogenous osteomyelitis are reported by Caldwell and Wickstrom.[1] The ages of the patients ranged from 18 days to 24 years, 96 per cent being under the age of 21 years. Among 58 cases in which the infecting organism was determined, hemolytic *Staphylococcus aureus* was found in 83 per cent and nonhemolytic *Staph. aureus* in 7 per cent. Positive blood cultures were obtained in 21 cases. The femur was involved in 28 cases, the tibia in 24, the humerus in 9, the fibula in 5, the radius in 3, the ulna in 2, the patella in 2, and the os calcis and the ilium in 1 each; a total of 75 bony lesions in 67 cases. Penicillin was given intramuscularly, 30,000 to 50,000 units every three or four hours to a total dosage of 920,000 to 8,640,000 units. Aspiration of local abscesses with instillation of penicillin solution into the aspirated cavity was also carried out every 24 or 48 hours, the total amount of penicillin per patient given this way ranging from 200,000 to 6,600,000 units. The duration of penicillin therapy ranged from 8 to 48 days, average 24 days. In 62 of the 75 lesions (82 per cent) the results were excellent or good. The greatest number of excellent and good results occurred in those patients who received penicillin within five days of the onset of the illness. It is concluded that in view of the excellent results obtained by the closed methods of treatment, it would appear unnecessary to drain localized abscesses surgically, with the possible exception of a few extensive abscesses associated with detached sequestra.

1. Caldwell, G. A. and Wickstrom, J.: The Closed Treatment of Acute Hematogenous Osteomyelitis, *Ann. Surg.*, **131**:734 (May) 1950.